The American Journal of Cardiology

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In hypertension

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P, 24, 215

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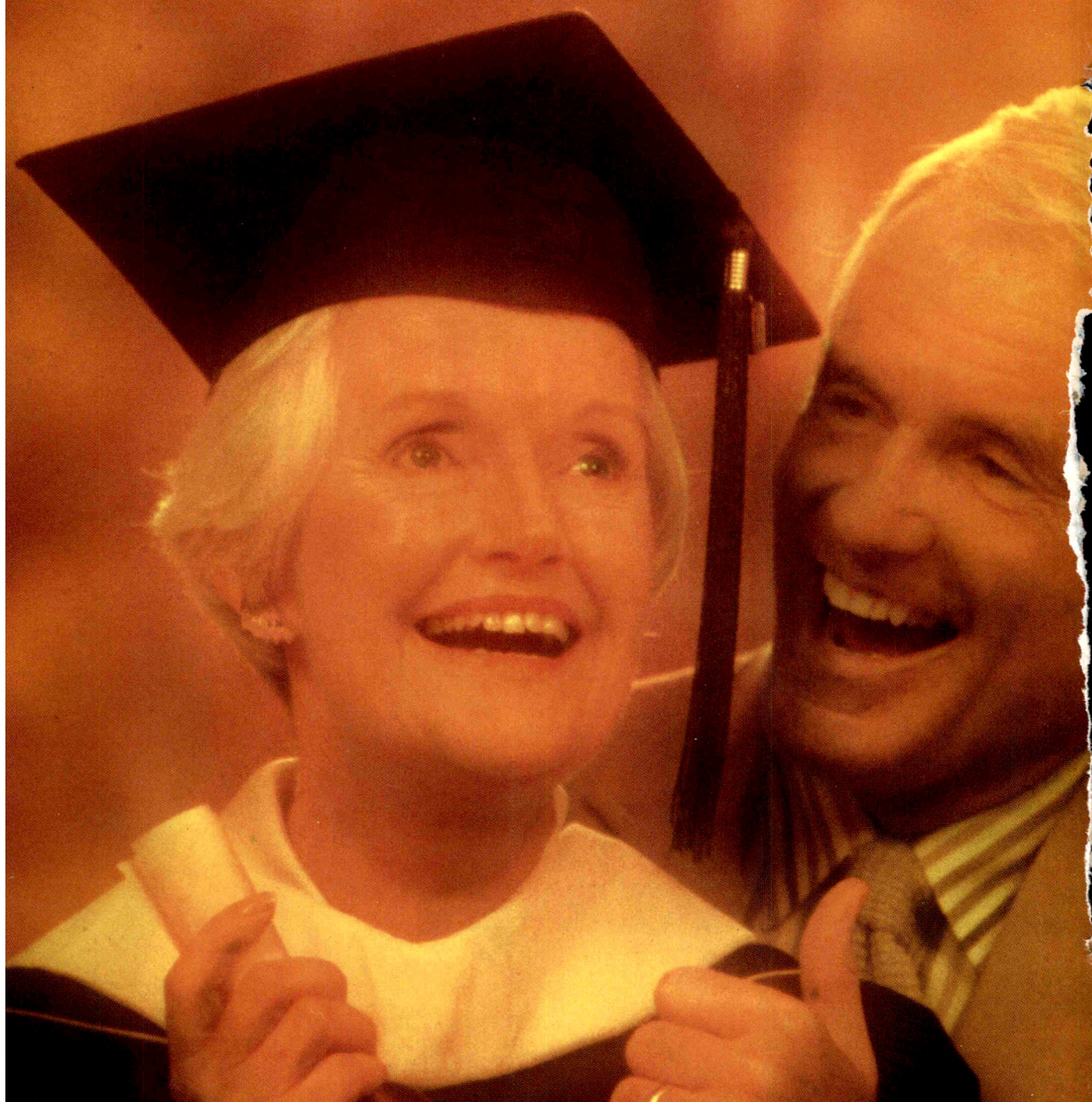
PREVENTIVE CARDIOLOGY

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Gemfibrozil-Lovastatin Therapy for Primary Hyperlipoproteinemias
Charles J. Glueck, Nancy Oakes, James Speirs, Trent Tracy, and James Lang

The specific aim of this retrospective, observational study was to assess the safety and efficacy of long-term (21 months/patient), open-label, gemfibrozil-lovastatin treatment in 80 patients with primary and, for the most part, combined hyperlipoproteinemia (68% of whom had already sustained atherosclerotic vascular disease). With gemfibrozil-lovastatin, mean total cholesterol decreased 22%, triglyceride levels decreased 35%, low-density lipoprotein cholesterol decreased 26%, and the total cholesterol/high-density lipoprotein cholesterol ratio decreased 24% (all p ≤0.0001). Myositis, symptomatic enough to discontinue gemfibrozil-lovastatin and attributable to 2-drug treatment, occurred in 3% of patients, and in 1% with concurrent high creatine phosphokinase (769 U/liter); no patient had rhabdomyolysis or myoglobinuria. While mandating careful follow-up with serial creatine phosphokinase and liver function tests in reliable patients with combined hyperlipidemia who are unable to respond optimally to 1-drug therapy, gemfibrozil-lovastatin treatment is safe and effective, reducing total and low-density lipoprotein cholesterol and elevating high-density lipoprotein cholesterol to levels at which regression of coronary artery disease may occur.

CORONARY ARTERY DISEASE

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Comparison of Delay Times to Hospital Presentation for Physicians and Nonphysicians with Acute Myocardial Infarction
Paul M. Ridker, JoAnn E. Manson, Samuel Z. Goldhaber, Charles H. Hennekens, and Julie E. Buring

To evaluate whether patients who recognize the symptoms of ischemia and have easy access to medical care have shortened time delays between onset of symptoms and hospital presentation, the total time interval between symptom onset and hospital arrival for 258 U.S. male physicians experiencing a first acute myocardial infarction (AMI) in the Physicians' Health Study (PHS) was compared with that of a comparable group of

VASCOR® (bepridil hydrochloride)

Tablets For Oral Administration

Brief Summary

INDICATIONS AND USAGE
Chronic Stable Angina (Classic Effort-Associated Angina)
VASCOR (bepridil hydrochloride) is indicated for the treatment of chronic stable angina (classic effort-associated angina). Because VASCOR has caused serious ventricular arrhythmias, including torsades de pointes type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to, or are intolerant of, other anti-anginal medication.

VASCOR may be used alone or in combination with beta blockers and/or nitrates. Controlled clinical studies have shown an added effect when VASCOR is administered to patients already receiving propranolol.

CONTRAINDICATIONS
VASCOR (bepridil hydrochloride) is contraindicated in patients with a known sensitivity to bepridil hydrochloride.

VASCOR is contraindicated in (1) patients with a history of serious ventricular arrhythmias (see WARNINGS–induction of New Serious Arrhythmias), (2) patients with sick sinus syndrome or patients with second- or third-degree AV block, except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients with uncompensated cardiac insufficiency, (5) patients with congenital QT interval prolongation (see WARNINGS), and (6) patients taking other drugs that prolong QT interval (see PRECAUTIONS-Drug Interactions).

WARNINGS
Induction of New Serious Arrhythmias
VASCOR (bepridil hydrochloride) has Class 1 anti-arrhythmic properties and, like other such drugs, can induce new arrhythmias, including VT/VF. In addition, because of its ability to prolong the QT interval, VASCOR can cause torsades de pointes type ventricular tachycardia. Because of these properties VASCOR should be reserved for patients in whom other anti-anginal agents do not offer a satisfactory effect.

In US clinical trials, the QT and QTc intervals were commonly prolonged by VASCOR in a dose-related fashion. While the mean prolongation of QTc was 8% and of QT was 10%, QTc increases of 25% or more were not uncommon, 5%; 8.7% QT. Increased QT and QTc may be associated with torsades de pointes type VT, which was seen at least briefly, in about 1.0% of patients in US trials; in many cases, however, patients with marked prolongation of QTc were taken off VASCOR therapy. All of the US patients with torsades de pointes had a prolonged QT interval and relatively low serum potassium. French marketing experience has reported over one hundred verified cases of torsades de pointes. While this number, based on total use, represents a rate of only 0.01%, the true rate is undoubtedly much higher, as spontaneous reporting systems all suffer from substantial under reporting.

Torsades de pointes is a polymorphic ventricular tachycardia often but not always associated with a prolonged QT interval, and often drug induced. The relation between the degree of QT prolongation and the development of torsades de pointes is not linear and the likelihood of torsades appears to be increased by hypokalemia, use of potassium wasting diuretics, and the presence of antecedent bradycardia. While the safe upper limit of QT is not defined, it is suggested that the interval not be permitted to exceed 0.52 seconds during treatment. If dose reduction does not eliminate the excessive prolongation, VASCOR should be stopped.

Because most domestic and foreign cases of torsades have developed in patients with hypokalemia, usually related to diuretic use or significant liver disease, if concomitant diuretics are needed, low doses and addition or primary use of a potassium sparing diuretic should be considered and serum potassium should be monitored.

VASCOR has been associated with the usual range of pro-arrhythmic effects characteristic of Class 1 anti-arrhythmics (increased premature ventricular contraction rates, new sustained VT, and VT/VF that is more difficult than previously to convert to sinus rhythm). Use in patients with severe arrhythmias (who are most susceptible to certain pro-arrhythmic effects) has been limited, so that risk in these patients is not defined.

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic nonlife-threatening ventricular arrhythmias who had myocardial infarctions more than six days but less than two years previously, an excess mortality/non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The applicability of these results to other populations (e.g., those without recent myocardial infarction) or to other anti-arrhythmic drugs is uncertain, but at present it is prudent to consider any drug documented to provoke new serious arrhythmias or worsening of preexisting arrhythmias as having a similar risk and to avoid their use in the post-infarction period.

Agranulocytosis: In US clinical trials of over 800 patients treated with VASCOR for up to five years, two cases of marked leukopenia and neutropenia were reported. Both patients were diabetic and elderly. One died with overwhelming gram-negative sepsis, itself a possible cause of marked leukopenia. The other patient recovered rapidly when VASCOR was stopped.

Congestive Heart Failure: Congestive heart failure has been observed infrequently (about 1%) during US controlled clinical trials, but experience with the use of VASCOR in patients with significantly impaired ventricular function is limited. There is little information on the effect of concomitant administration of VASCOR and digoxin; therefore, caution should be exercised in treating patients with congestive heart failure.

Hepatic Enzyme Elevation: In US clinical studies with VASCOR in about 1000 patients and subjects, clinically significant (at least 2 times the upper limit of normal) transaminase elevations were observed in approximately 1% of the patients. None of these patients became clinically symptomatic or jaundiced and values returned to normal when the drug was stopped.

Hypokalemia: In clinical trials VASCOR has not been reported to reduce serum potassium levels. Because hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency should be corrected before VASCOR therapy is initiated and normal potassium concentrations should be maintained during VASCOR therapy. Serum potassium should be monitored periodically.

PRECAUTIONS
General
Caution should be exercised when using VASCOR (bepridil hydrochloride) in patients with left bundle branch block or sinus bradycardia (less than 50 b.p.m.). Care should also be exercised in patients with serious hepatic or renal disorders because such patients have not been studied and bepridil is highly metabolized, with metabolites excreted primarily in the urine.

Recent Myocardial Infarction
In US clinical trials with VASCOR, patients with myocardial infarctions within three months prior to initiation of drug treatment were excluded. The initiation of VASCOR therapy in such patients, therefore, cannot be recommended.

Information for Patients
Since QT prolongation is not associated with defined symptomatology, patients should be instructed on the importance of any potassium supplementation or potassium sparing diuretic, and the need for routine electrocardiograms and periodic monitoring of serum potassium. The following Patient Information is printed on the carton label of each unit of use bottle of 30 tablets:

As with any medication that you take, you should notify your physician of any changes in your overall condition. Insure that you follow your physician's instructions regarding follow-up visits. Please notify any physician who treats you for a medical condition that you are taking VASCOR* (bepridil hydrochloride), as well as any other medications.

Drug Interactions
Nitrates: The concomitant use of VASCOR with long- and short-acting nitrates has been safely tolerated in patients with stable angina pectoris. Sublingual nitroglycerin may be taken if necessary for the control of acute angina attacks during VASCOR therapy.

Beta-blocking Agents: The concomitant use of VASCOR and beta-blocking agents has been well tolerated in patients with stable angina. Available data are not sufficient, however, to predict the effects of concomitant medication on patients with impaired ventricular function or cardiac conduction abnormalities (see DOSAGE AND ADMINISTRATION).

Digoxin: In controlled studies in healthy volunteers, bepridil hydrochloride either had no effect (one study) or was associated with modest increases, about 30% (two studies) in steady-state serum digoxin concentrations. Limited clinical data in angina patients receiving concomitant bepridil hydrochloride and digoxin therapy indicate no discernible changes in serum digoxin levels. Available data are neither sufficient to rule out possible increases in serum digoxin with concomitant treatment in some patients, nor other possible interactions, particularly in patients with cardiac conduction abnormalities (also see WARNINGS-Congestive Heart Failure).

Oral Hypoglycemics: VASCOR has been safely used in diabetic patients without significantly lowering their blood glucose levels or altering their need for insulin or oral hypoglycemic agents.

General Interactions: Certain drugs could increase the likelihood of potentially serious adverse effects with bepridil hydrochloride. In general, these are drugs that have one or more pharmacologic activities similar to bepridil hydrochloride, including anti-arrhythmic agents such as quinidine and procainamide, cardiac glycosides and tricyclic anti-depressants. Anti-arrhythmics and tricyclic anti-depressants could exaggerate the prolongation of the QT interval observed with bepridil hydrochloride. Cardiac glycosides could exaggerate the depression of AV nodal conduction observed with bepridil hydrochloride.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenicity was revealed in one lifetime study in mice at dosages up to 60 times (for a 60 kg subject) the maximum recommended dosage in man. Unilateral follicular adenomas of the thyroid were observed in a study in rats following lifetime administration of high doses of bepridil hydrochloride, i.e., ≥ 100 mg/kg/day (20 times the usual recommended dose in man). No mutagenic or other genotoxic potential of bepridil hydrochloride was found in the following standard laboratory tests: the Micronucleus Test for Chromosomal Effects, the Liver Microsome Activated Bacterial Assay for Mutagenicity, the Chinese Hamster Ovary Cell Assay for Mutagenicity, and the Sister Chromatid Exchange Assay. No intrinsic effect on fertility by bepridil hydrochloride was demonstrated in rats.

In monkeys, at 200 mg/kg/day, there was a decrease in testicular weight and spermatogenesis. There were no systematic studies in man related to this point. In rats, at doses up to 300 mg/kg/day, there was no observed alteration of mating behavior nor of reproductive performance.

Usage in Pregnancy
Pregnancy Category C. Reproductive studies (fertility and peri-postnatal) have been conducted in rats. Reduced litter size at birth and decreased pup survival during lactation were observed at maternal dosages 37 times (on a mg/kg basis) the maximum daily recommended therapeutic dosage.

In teratology studies, no effects were observed in rats or rabbits at these same dosages. There are no well-controlled studies in pregnant women. Use VASCOR in pregnant or nursing women only if the potential benefit justifies the potential risk.

Nursing Mothers
Bepridil is excreted in human milk. Bepridil concentration in human milk is estimated to reach about one third the concentration in serum. Because of the potential for serious adverse reactions in nursing infants from VASCOR a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of VASCOR in children have not been established.

ADVERSE REACTIONS
Adverse reactions were assessed in 529 patients who received VASCOR (bepridil hydrochloride) in controlled trials of 4-12 weeks duration and longer-term uncontrolled studies. The most common side effects occurring more frequently than in control groups were upper gastrointestinal complaints (nausea, dyspepsia or GI distress) in about 22%, diarrhea in about 8%, dizziness in about 15%, asthenia in about 10% and nervousness in about 7%. The adverse reactions seen in at least 2% of bepridil patients in controlled trials are shown in the following list.

Body as a Whole: Asthenia, Headache, Flu Syndrome **Cardiovascular/Respiratory:** Palpitations, Dyspnea, Respiratory infection **Gastrointestinal:** Dyspepsia, G.i. Distress, Nausea, Dry Mouth, Anorexia, Diarrhea, Abdominal Pain, Constipation **Central Nervous System:** Drowsy, Insomnia, Dizziness, Tremor, Tremor of Hand, Paresthesia **Psychiatric:** Nervous **Special Senses:** Tinnitus.

About 15% of patients however, left bepridil treatment because of adverse experiences. In controlled clinical trials, these were principally gastrointestinal (1.0%), dizziness (1.0%), ventricular arrhythmias (1.0%) and syncope (0.6%).

Across all controlled and uncontrolled trials, VASCOR was evaluated in over 800 patients with chronic angina. In addition to the adverse reactions noted above, the following were observed in 0.5 to 2.0% of the VASCOR patients or are rarer, but potentially important events seen in clinical studies or reported in post marketing experience. In most cases it is not possible to determine whether there is a causal relationship to bepridil treatment.

Body as a Whole: Fever, pain, myalgic asthenia, superinfection, flu syndrome. **Cardiovascular/Respiratory:** Sinus tachycardia, sinus bradycardia, hypertension, vasodilation, edema, ventricular premature contractions, ventricular tachycardia, prolonged QT interval, rhinitis, cough, pharyngitis. **Gastrointestinal:** Flatulence, gastritis, appetite increase, dry mouth, constipation. **Musculoskeletal:** Arthritis. **Central Nervous System:** Fainting, vertigo, akathisia, drowsiness, insomnia, tremor. **Psychiatric:** Depression, anxiousness, adverse behavior effect. **Skin:** Rash, sweating, skin irritation. **Special Senses:** Blurred vision, tinnitus, taste change. **Urogenital:** Loss of libido, impotence. **Abnormal Lab Values:** Abnormal liver function test, SGPT increase.

Certain cardiovascular events, such as acute myocardial infarction (about 3% of patients) worsened heart failure (1.9%), worsened angina (4.5%), severe arrhythmia (about 2.4% VT/VF) and sudden death (1.6%) have occurred in patients receiving bepridil, but have not been included as adverse events because they appear to be, and cannot be distinguished from, manifestations of the patient's underlying cardiac disease. Such events as torsades de pointes arrhythmias, prolonged QT/QTc, bradycardia, first degree heart block, which are probably related to bepridil, are included in the tables.

OVERDOSAGE
In the event of overdosage, we recommend close observation in a cardiac care facility for a minimum of 48 hours and use of appropriate supportive measures in addition to gastric lavage. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase transmembrane calcium ion influx. Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Ventricular tachycardia should be handled by cardioversion and, if persistent, by overdrive pacing. There has been one experience with overdosage in which a patient inadvertently took a single dose of 1600 mg of VASCOR (bepridil hydrochloride). The patient was observed for 72 hours in intensive care, but no significant adverse experiences were noted.

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240 men enrolled in the U.S. component of the Second International Study of Infarct Survival (ISIS-2), as well as with those of previously published series of patients with AMI. Overall, the median delay time for physicians having a first AMI was 1.8 hours, which was significantly shorter than that for nonphysicians in ISIS-2 or in any prior study (p <0.001). Although conclusions based on these observational data are speculative, this difference may help explain the far lower than expected cardiovascular mortality rates among physician participants in the PHS. Furthermore, the data provide encouraging evidence that shorter delay times from onset of symptoms to hospital presentation can be achieved.

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Noninvasive Identification of Severe Coronary Artery Disease Using Exercise Tomographic Thallium-201 Imaging

Timothy F. Christian, Todd D. Miller, Kent R. Bailey, and Raymond J. Gibbons

Exercise thallium-201 tomographic imaging was performed in 688 patients who had coronary angiography within 6 months. There were significant differences in clinical, exercise and thallium-201 imaging variables for patients with and without 3-vessel or left main coronary artery disease (CAD). However, using multiple logistic regression analysis, only 4 variables were independently predictive of left main or 3-vessel CAD — the magnitude of ST-segment depression with exercise, the number of visually abnormal short-axis thallium-201 segments, diabetes and the change in systolic blood pressure with exercise. Using these 4 variables, nomograms were developed to classify patients according to the probability of severe CAD. The prevalence of 3-vessel or left main CAD was 12% in the low-probability group, 22% in the intermediate group, and 52% in the high-probability group. These nomograms should be of clinical value when interpreting tomographic thallium-201 exercise studies.

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Effect of Thrombolytic Therapy on the Predictive Value of Signal-Averaged Electrocardiography After Acute Myocardial Infarction

Marek Malik, Piotr Kulakowski, Olusola Odemuyiwa, Jan Poloniecki, Anne Staunton, Teri Millane, Thomas Farrell, and A. John Camm

Standard time domain variables of signal-averaged electrocardiography in 331 survivors of acute myocardial infarction were examined. Of these subjects, 130 received early thrombolytic therapy. There were 17 serious arrhythmic events in the group without thrombolysis, and 8 in those with thrombolysis. Statistically, highly significant differences between the signal-averaged electrocardiographic variables of patients with and without arrhythmic events were found only in the group without thrombolysis. When using 2 previously published categoric criteria for the diagnosis of abnormal signal-averaged electrocardiography, their positive predictive accuracy of predicting the arrhythmic events was >3 times higher in the group without thrombolysis. Retrospectively adjusted receiver-operator characteristics showed that for the sensitivity of 30%, the maximum achievable positive predictive accuracy of signal-averaged electrocardiographic prediction of arrhythmic events was 100% in the group without thrombolysis, and 27% in those with thrombolysis. Thus, standard signal-

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averaged electrocardiography after myocardial infarction is less informative in patients who received thrombolytic treatment.

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Six-Year Survival After Coronary Thrombolysis and Early Revascularization for Acute Myocardial Infarction

George J. Taylor, H. Weston Moses, Richard E. Katholi, Cynthia Korsmeyer, Paul Kolm, James T. Dove, Frank L. Mikell, Joseph M. Sutton, Harry A. Wellons, and Joel A. Schneider

Six-year follow-up was conducted in a consecutive series of 192 patients treated with thrombolytic therapy for acute myocardial infarction with ST-segment elevation. Cardiac mortality was 6% in the hospital and 9% for survivors of hospitalization. A closed infarct artery at catheterization, diabetes mellitus and anterior myocardial infarction predicted cardiac death during follow-up.

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Value of Negative Predischarge Exercise Testing in Identifying Patients at Low Risk After Acute Myocardial Infarction Treated by Systemic Thrombolysis

Giacomo Piccalò, Salvatore Pirelli, Daria Massa, Manlio Cipriani, Filippo Maria Sarullo, and Claudio De Vita

To verify the value of negative predischarge exercise tests in identifying low-risk patients treated with thrombolysis after acute myocardial infarction (AMI), 157 consecutive patients underwent maximal or symptom-limited exercise testing within 15 days of AMI. All patients were followed for 6 months. Death and nonfatal reinfarction were considered as major coronary events, and recurrence of angina as a minor event. Exercise test results were negative in 105 patients and positive for angina or ST depression ≥ 0.1 mV in 52. By the end of follow-up, 90% of the patients with negative exercise test results were event-free (97% had no major events). These results show that thrombolytic therapy does not affect the value of negative postinfarction exercise testing in identifying low-risk patients.

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Magnetic Resonance Imaging During Dobutamine Stress in Coronary Artery Disease

Dudley J. Pennell, S. Richard Underwood, Carla C. Manzara, R. Howard Swanton, J. Malcolm Walker, Peter J. Ell, and Donald B. Longmore

Magnetic resonance imaging (MRI) has been limited in the investigation of coronary artery disease, because of difficulty in obtaining images during exercise. Therefore, an infusion of dobutamine was used to study 25 patients with angina. Areas of abnormal wall motion were compared with thallium myocardial perfusion tomograms and coronary arteriography. Of 22 patients with significant coronary artery disease, 21 (96%) had reversible myocardial perfusion defects, and 20 (91%) had reversible wall motion abnormalities. Comparison of abnormal segments of perfusion and wall motion showed 96% agreement at rest, 90% agreement during stress, and 91% agreement for the assessment of functional reversibility. The magnetic resonance signal decreased in ischemic segments (-67 units [9.2%]; $p < 0.05$). Dobutamine is ideal as a stress agent for MRI because of

its short half-life, and these results suggest that it is more effective in the provocation of wall motion abnormalities than is dipyridamole.

To assess the effect of the addition of atropine to dobutamine stress echocardiography in patients with negative stress echocardiograms, and who did not achieve 85% predicted maximal heart rate during dobutamine alone, 49 patients who received atropine in addition to dobutamine were compared with 31 who achieved an adequate heart rate or positive test with dobutamine alone. The addition of atropine caused a significant increase in heart rate, achieving comparable peak heart rates, and resulted in similar sensitivities and specificities for the detection of coronary artery disease for the 2 groups without serious complications.

The clinical experience with restenosis after elective percutaneous transluminal coronary angioplasty (PTCA) was reviewed in 1,490 patients without prior PTCA or coronary bypass surgery. When restenosis was documented, 363 were treated medically, 1,051 with repeat PTCA, and 76 with coronary bypass surgery. Two patients who underwent coronary bypass surgery had Q-wave myocardial infarction with no deaths. In patients who had undergone repeat PTCA there were 778 with 1-vessel and 273 with multiple vessel disease. Re-dilatation of restenotic sites was performed in 95%, with a 99% angiographic success. Coronary bypass surgery was required in 2.5%. One patient with multiple vessel disease died. Actuarial 5-year survival was 95%. By the 5-year point, most patients had repeat revascularization or an event. Survival correlated with age and diabetes mellitus. At 5 years, survival without diabetes was 97, and 83% with diabetes (p = 0.0002). By carefully selecting therapy, excellent initial results and long-term prognosis may be achieved.

The value of a postoperative exercise test for predicting cardiac events after coronary artery bypass grafting (CABG) was prospectively studied in 231 consecutive, angiographically controlled patients. During a 5-year follow-up there were 28 cardiac events (12%). The rate of graft patency did not differ between groups with and without cardiac events, but ejection

fraction was lower in patients with cardiac events. Duration of the exercise test was shorter, and maximal work load was lower in patients with cardiac events, but in the multivariate Cox regression model, no exercise variable had predictive value for future cardiac events. The predictive value of a postoperative exercise test appears to be limited, and signs of left ventricular dysfunction are of greater significance for the 5-year prognosis after CABG.

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Comparison of Patient-Reported Outcomes After Elective Coronary Artery Bypass Grafting in Patients Aged ≥ and <65 Years

Edward Guadagnoli, John Z. Ayanian, and Paul D. Cleary

The elderly represent a growing proportion of patients undergoing coronary artery bypass graft (CABG). Although functional benefits after CABG have been demonstrated in younger patients, little is known about the impact of CABG on the elderly. A number of postsurgical (6 months) health-related quality-of-life outcomes reported by patients aged < and ≥65 years who underwent elective CABG at 4 major teaching hospitals were compared. Older patients reported functional benefits similar to those reported by younger ones, and the factors associated with better functioning did not vary by age group.

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Increased Onset of Sudden Cardiac Death in the First Three Hours After Awakening

Stefan N. Willich, Robert J. Goldberg, Malcolm Maclure, Lucy Perriello, and James E. Muller

A circadian variation of sudden cardiac death has been documented, but its relation to individual time of awakening and possible triggering events has not been studied in the general population. The time of day of 94 cases of sudden cardiac death (mean age 61 ± 9 years, 74% men), identified by monitoring of mortality records in 4 city halls in Massachusetts, demonstrated a circadian variation ($p < 0.05$) with a peak from 9:00 A.M. to 12:00 noon. An analysis of time of death adjusted for individual waketimes of the decedents demonstrated an increased onset of sudden cardiac death during the initial 3-hour interval after awakening with a relative risk of 2.6 (95% confidence interval 1.6, 4.2) compared with other times of the day. The increased risk of sudden cardiac death soon after awakening suggests specific triggering factors or mechanisms that are particularly likely to occur during this time and indicates the need to reevaluate preventive strategies.

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

*CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.

Please see brief summary, including the **boxed WARNING regarding Use in Pregnancy,** on the last page of this ad.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Effectiveness of Loading Oral Flecainide for Converting Recent-Onset Atrial Fibrillation to Sinus Rhythm in Patients Without Organic Heart Disease or With Only Systemic Hypertension

Alessandro Capucci, Tiziano Lenzi, Giuseppe Boriani, Giuseppe Trisolino, Nicola Binetti, Mario Cavazza, Giovanni Fontana, and Bruno Magnani

Sixty-two patients with recent-onset atrial fibrillation (New York Heart Association functional class 1 and 2) were randomized to treatment with flecainide (single oral loading dose), amiodarone (intravenous bolus followed by intravenous infusion) or placebo. The rate of conversion to sinus rhythm within 8 hours was statistically higher with flecainide (91% of patients) than with amiodarone (37%) or placebo (48%). Resumption of sinus rhythm within 24 hours occurred in 95% of patients treated with flecainide and in 89% treated with amiodarone. No major side effects occurred. In conclusion, flecainide administered orally in a single loading dose is highly effective in converting recent-onset atrial fibrillation to sinus rhythm and is more rapid than is intravenous amiodarone. This in-hospital regimen was safe and well-tolerated.

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Electrocardiographic Changes and Arrhythmias After Cancer Therapy in Children and Young Adults

Ranae L. Larsen, Regina I. Jakacki, Victoria L. Vetter, Anna T. Meadows, Jeffrey H. Silber, and Gerald Barber

Whereas acute electrocardiographic changes and arrhythmias can occur during cancer therapy with anthracyclines or mediastinal irradiation, the chronic effect of these therapies in children is unknown. Twelve-lead and 24-hour electrocardiograms were recorded to study the late effects of these therapies in 134 children and young adults. The frequency of atrioventricular block, corrected QT interval >0.44, abnormal Q waves, and supraventricular and ventricular arrhythmias were increased compared with results in age-matched normal subjects. Most patients had abnormalities limited to single supraventricular or ventricular premature complexes; however, potentially serious ventricular ectopies, including ventricular pairs and ventricular tachycardia were noted in patients with cumulative doses >200 mg/m^2. In patients treated in childhood for cancer, electrocardiographic changes and arrhythmias are not limited to the acute phase of cardiac toxicity. Survivors who have received anthracyclines or cardiac irradiation should undergo ambulatory electrocardiography as part of their long-term follow-up care.

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Stimulation of the Summit of the Right Ventricular Aspect of the Ventricular Septum During Orthodromic Atrioventricular Reentrant Tachycardia

Jeffrey Goldberger, Yinshi Wang, and Melvin Scheinman

Application of ventricular premature complexes (VPCs) from the right ventricular (RV) apex during orthodromic atrioventricular (AV) reentrant tachycardia has limitations both in the ability to shorten the succeeding atrial cycle length and in helping to identify accessory pathway location. Stimulation from the summit of the RV septum during AV reentrant tachycardia was investigated as a new technique to improve the diagnostic use of applying VPCs during AV reentrant tachycardia. Stimulation of the summit of the RV septum improves the ability of VPCs to shorten the atrial cycle length during AV reentrant tachycardia. This improvement is most marked in patients with left free wall accessory pathways, but is also evident in those with posteroseptal accessory pathways.

SYSTEMIC HYPERTENSION

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Silent Myocardial Ischemia in Men With Systemic Hypertension and Without Clinical Evidence of Coronary Artery Disease

David Siegel, Melvin D. Cheitlin, Dana G. Seeley, Dennis M. Black, and Stephen B. Hulley

The prevalence, characteristics and circadian pattern of silent myocardial ischemia on 24-hour Holter monitoring, and its association with ventricular arrhythmias was studied in hypertensive men aged 35 to 70 years (mean 61) without clinical cardiac disease. Silent myocardial ischemia occurred in 50 of 186 men (27%) and lasted from 2 to 289 minutes (mean 30 and median 18). Men were less likely to have silent myocardial ischemia from midnight to 6 A.M. than at other times of the day. There was little difference in the proportion of men with ventricular arrhythmias compared to those without silent myocardial ischemia. These findings suggest that silent myocardial ischemia occurs in approximately 25% of an older population of hypertensive men without clinical cardiac disease and that the circadian pattern of silent ischemic episodes in men free of clinical cardiac disease is similar to that reported for patients with cardiac disease.

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Effects of Combined Hydrochlorothiazide and Amiloride Versus Single Drug on Changes in Salt Taste and Intake

Richard D. Mattes and Karl Engelman

Hydrochlorothiazide stimulates salt intake without altering salivary or gustatory function. Amiloride reportedly reduces salivary sodium levels and salt taste. It was hypothesized that these unintended drug actions would be attenuated by concurrent use of these 2 diuretics. Normotensive adults (n = 23) were administered placebo for 2 weeks, active combination drug Moduretic® for 4 weeks, and placebo again for 2 weeks in a

double-blind protocol. Salivary flow, gustatory function and sodium intake were monitored at the end of each period, together with selected physiologic measures (i.e., plasma aldosterone, plasma renin activity, body composition, blood pressure and heart rate). No significant changes were observed for salivary flow, salt taste or sodium intake. These findings indicate that amiloride and hydrochlorothiazide used in combination can reduce drug effects that may compromise the efficacy of either drug when used alone.

METHODS

This study investigated whether the combination of 2 computer programs for the interpretation of the electrocardiogram (ECG) and of the vectorcardiogram (VCG) would yield a better diagnostic result than either one separately. This would require that a VCG always be recorded in addition to the ECG. To circumvent this complication, the VCG was reconstructed from the ECG. This reconstructed VCG was then interpreted by the VCG program, whereupon the interpretations of ECG and reconstructed VCG were combined. The combination of the ECG and VCG interpretations yielded a better diagnostic result than each interpretation separately. The performance of the combined interpretations of the ECG and reconstructed VCG is similar to that of the combined ECG and VCG. Thus, the performance of an ECG computer program can be improved by incorporating both ECG and VCG classificatory knowledge, using only the ECG itself.

EDITORIALS

BRIEF REPORTS

PREVENTIVE CARDIOLOGY

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Gemfibrozil-Lovastatin Therapy for Primary Hyperlipoproteinemias

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Trent Tracy, PA, and James Lang, MD

The specific aim of this retrospective, observational study was to assess safety and efficacy of long-term (21 months/patient), open-label, gemfibrozil-lovastatin treatment in 80 patients with primary mixed hyperlipidemia (68% of whom had atherosclerotic vascular disease). Because ideal lipid targets were not reached (low-density lipoprotein (LDL) cholesterol <130 mg/dl, high-density lipoprotein (HDL) cholesterol >35 mg/dl, or total cholesterol/HDL cholesterol <4.5 mg/dl) with diet plus a single drug, gemfibrozil (1.2 g/day)-lovastatin (primarily 20 or 40 mg) treatment was given. Follow-up visits were scheduled with 2-drug therapy every 6 to 8 weeks, an average of 10.3 visits per patient, with 741 batteries of 6 liver function tests and 714 creatine phosphokinase levels measured. Only 1 of the 4,446 liver function tests (0.02%), a gamma glutamyl transferase, was ≥3 times the upper normal limit. Of the 714 creatine phosphokinase levels, 9% were high; only 1 (0.1%) was ≥3 times the upper normal limit. With 2-drug therapy, mean total cholesterol decreased 22% from 255 to 200 mg/dl, triglyceride levels decreased 35% from 236 to 154 mg/dl, LDL cholesterol decreased 26% from 176 to 131 mg/dl, and the total cholesterol/HDL cholesterol ratio decreased 24% from 7.1 to 5.4, all p ≤0.0001. Myositis, attributable to the drug combination and symptomatic enough to discontinue it, occurred in 3% of patients, and in 1% with concurrent high creatine phosphokinase (769 U/liter); no patients had rhabdomyolysis or myoglobinuria. Gemfibrozil-lovastatin treatment mandates careful clinical follow-up with serial creatine phosphokinase and liver function tests in reliable patients who (1) do not respond optimally to 1-drug therapy, (2) are well informed about possible myositis, and (3) are prepared to discontinue 2-drug therapy at earliest onset of myositis symptoms. Within this frame of reference, combined gemfibrozil-lovastatin treatment is safe and effective, reducing total and LDL cholesterol, triglycerides, and the total cholesterol/HDL cholesterol ratio to levels at which regression of coronary artery disease may occur.

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Reducing low-density lipoprotein (LDL) cholesterol and raising high-density lipoprotein (HDL) cholesterol by a variety of therapies reduces coronary heart disease morbidity and mortality, retards progression of coronary artery atherosclerosis, and often induces regression.[1-11] To lower LDL cholesterol and raise HDL cholesterol to optimal target levels (<130 mg/dl, >35 mg/dl),[12,13] 2-drug therapies are often required, particularly in high-risk patients with combined hyperlipidemias.[14-19] Gemfibrozil-lovastatin lowers LDL cholesterol and triglyceride levels and raises HDL cholesterol,[14-19] and is more effective than gemfibrozil-resin.[16] Nicotinic acid-resin and lovastatin-resin have been used primarily to lower LDL cholesterol[1,3,5,6]; lovastatin-nicotinic acid is rarely used because of hepatotoxicity and increased risk of rhabdomyolysis.[20] Gemfibrozil-lovastatin mandates very careful serial monitoring[14-19] because myopathy, rhabdomyolysis, myoglobinuria and renal injury have been reported,[21,22] particularly in patients receiving concomitant cyclosporine. Our specific aim in this retrospective, observational, and predominantly secondary prevention study was to assess the safety and efficacy of open-label therapy with diet, gemfibrozil and lovastatin in 80 patients with primary mixed hyperlipidemias over an average 2-drug treatment span of 21 months/patient.

METHODS

Patients: The 80 patients (50 men [age 54 ± 11 years], 30 women [age 60 ± 8 years]) had severe primary, and for the most part, mixed hyperlipidemias (high cholesterol, triglyceride, low HDL cholesterol)[14] (Figures 1 to 4); 68% had atherosclerotic vascular disease (Table I). There were 78 whites, 1 black and 1 other, all referred for diagnosis and therapy of hyperlipidemias in our outpatient cholesterol center. Hyperlipidemias secondary to drugs, excessive alcohol or diseases (nephrotic syndrome, poorly controlled diabetes mellitus, hypothyroidism, uremia, and so forth), were ruled out by history, physical examination and laboratory testing.[14]

Study design: This report represents a retrospective compilation of all patients with serial systematic follow-up in our cholesterol center who received gemfibrozil-lovastatin therapy, and who met the following 3 selection criteria:

1. Primary hyperlipoproteinemias.
2. Failure to achieve targeted lipid and lipoprotein cholesterol goals (total cholesterol <200 mg/dl, LDL cholesterol <130 mg/dl, HDL cholesterol >35 mg/dl,[13] total cholesterol/HDL cholesterol <4.5/1[15]) with diet and either gemfibrozil or lovastatin.

Criteria 1 and 2 were met by 71 patients, 20 initially taking lovastatin alone, and 51 initially taking gemfibrozil alone.

Nine patients with primary hyperlipidemias were also included who did not meet the 1 drug at baseline criterion, 5 who simultaneously began therapy with gemfibrozil and lovastatin at baseline after consultation with their family physicians, and 4 referred to us who were already taking gemfibrozil-lovastatin. These 9 patients were included in the analyses after finding no difference between changes (from baseline until the last visit) in their lipids and lipoproteins with 2-drug therapy compared to changes in the 71 patients originally taking single drug therapy (p >0.1).

Our current study does not include the 25 patients previously reported from our center on gemfibrozil-lovastatin for a mean of 12.5 months[15] to allow us to present entirely new, heretofore unpublished data.

3. Two-drug therapy with lovastatin and gemfibrozil for ≥6 months.

Eighty patients met all 3 of the aforementioned cri-
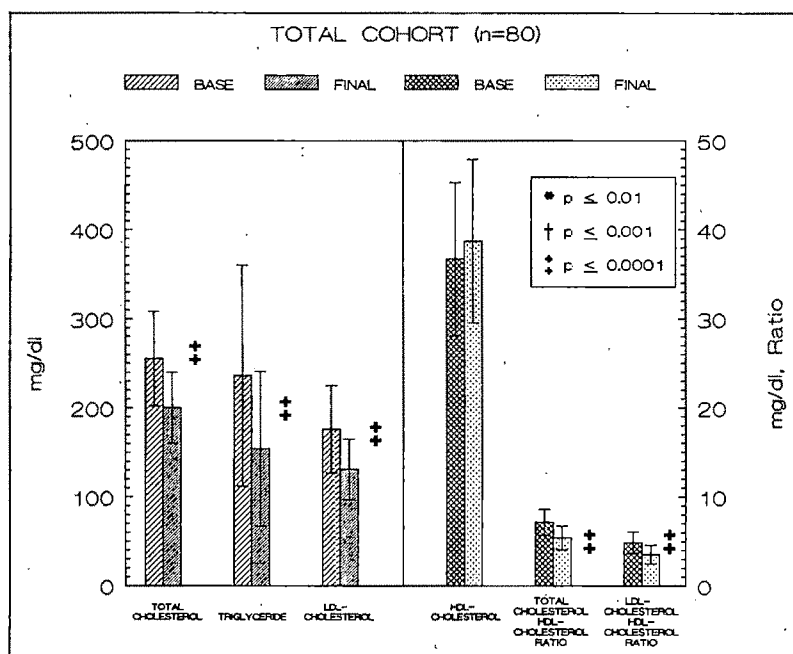
FIGURE 1. Mean (SD) baseline and (with gemfibrozil-lovastatin) final plasma total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (mg/dl), total cholesterol/HDL cholesterol ratio, and LDL/HDL cholesterol ratio in the total cohort (n = 80).
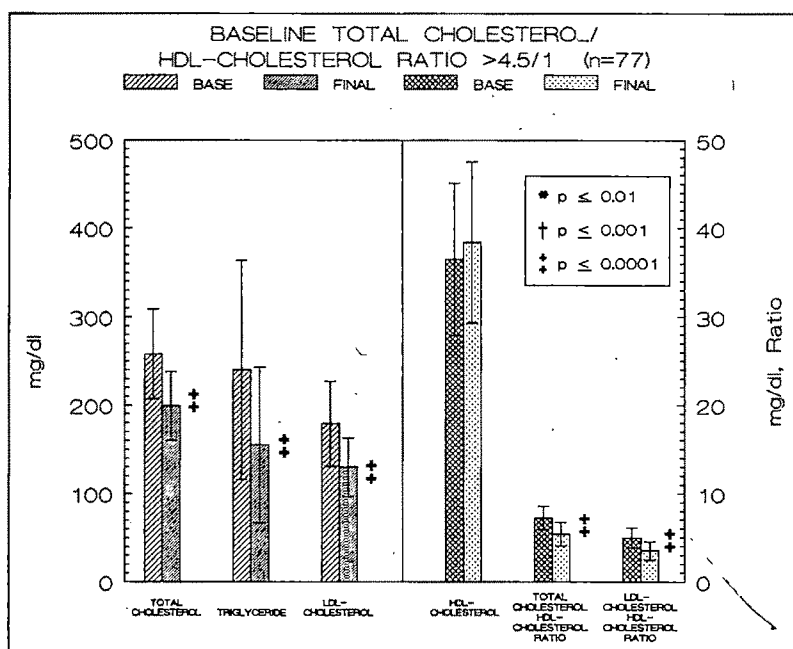
FIGURE 2. Mean (SD) baseline and (with gemfibrozil-lovastatin) final plasma total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (mg/dl), total cholesterol/HDL cholesterol ratio, and LDL/HDL cholesterol ratio in 77 patients with baseline total cholesterol/HDL cholesterol ratio >4.5/1.

teria, and received gemfibrozil-lovastatin for an average of 21 months (range of 6 to 40) (Figure 5) and 10.3 follow-up visits/patient. Ninety-two patients received gemfibrozil-lovastatin and met the first 2 criteria for study inclusion but not the third, who received 2-drug therapy within 6 months. To present an unbiased assessment of the reasons for stopping 2-drug therapy, we included, as a denominator, all 92 patients receiving gemfibrozil-lovastatin, irrespective of how long the 2-drug therapy had been continued.

Diet and combined gemfibrozil-lovastatin therapy: Because 68% of the patients had atherosclerotic vascular disease (Table I), we set the following target values with the goal of stopping atherosclerosis progression or initiating regression[1-7]: total cholesterol <200 mg/dl, LDL cholesterol <130 mg/dl, HDL cholesterol >35 mg/dl, total cholesterol/HDL cholesterol ratio <4.5/1.[1-7,13,15] Lipid levels were first stabilized with diet, primarily the American Heart Association's Step 1 and 2, or the National Institutes of Health Types IV or V.[15] Gemfibrozil, usually 1.2 g/day, was the initial lipid-lowering drug used in 51 patients who, with diet, retained high triglyceride or low HDL cholesterol, or both, often accompanied by high LDL cholesterol. Lovastatin, usually 20 mg/day, was administered as the initial lipid-lowering drug in 20 patients whose high LDL cholesterol predominated, often accompanied by low HDL cholesterol.

When target lipid-lipoprotein levels were not achieved with diet and 1-drug therapy, 2-drug therapy was begun (Table II). No attempt was made to randomize treatment to a placebo-controlled trial. We did

FIGURE 3. Mean (SD) baseline and (with gemfibrozil-lovastatin) final plasma total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (mg/dl), total cholesterol/HDL cholesterol ratio, and LDL/HDL cholesterol ratio in 49 patients with baseline HDL cholesterol <35 mg/dl in men and <40 mg/dl in women.
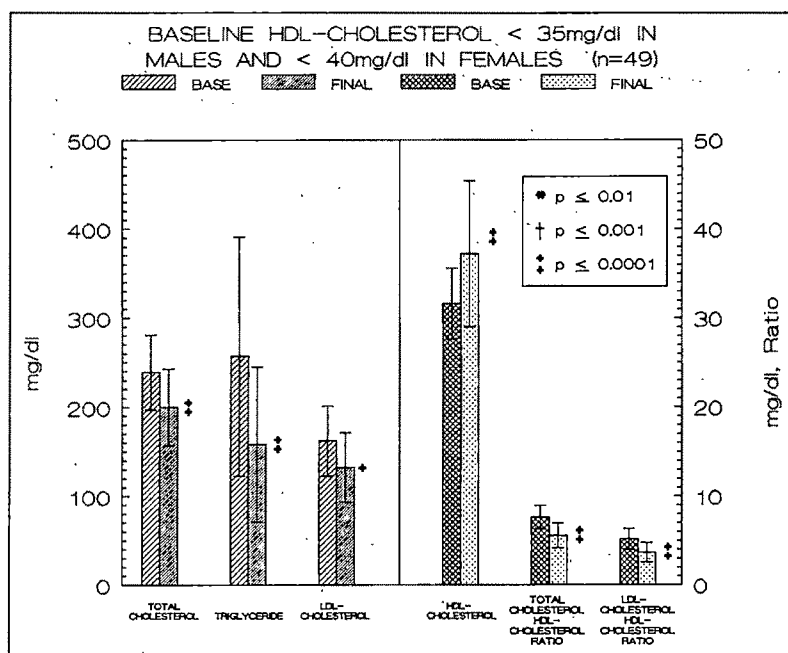
FIGURE 4. Mean (SD) baseline and (with gemfibrozil-lovastatin) final plasma total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (mg/dl), total cholesterol/HDL cholesterol ratio, and LDL/HDL cholesterol ratio in 28 patients with baseline total cholesterol >240 mg/dl and triglyceride >200 mg/dl.
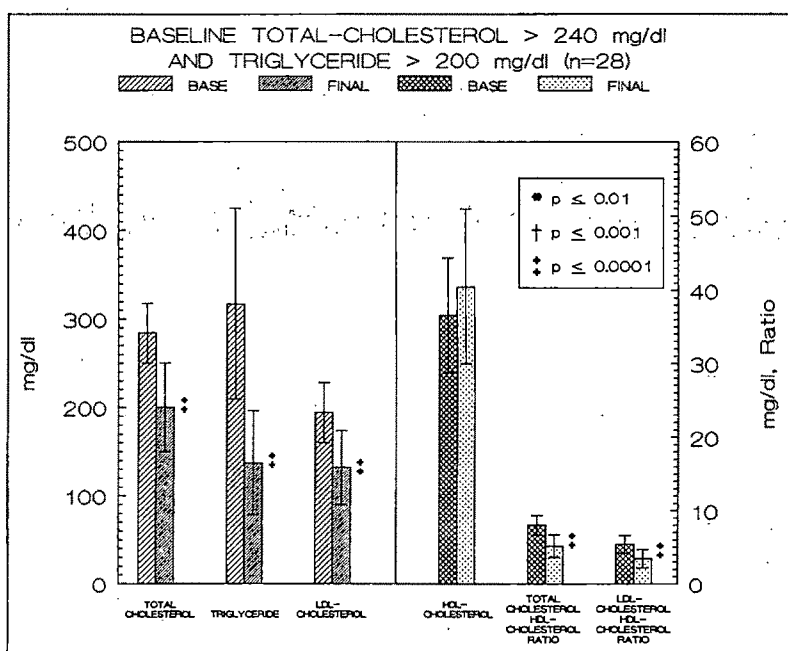
not follow a rigid stepwise dose regimen for lovastatin beyond trying to reach our lipid-lipoprotein targets[13,15] with the lowest lovastatin dose. Although our retrospective, observational, secondary prevention study cannot provide the confidence obtained from a prospective, randomized, controlled clinical trial, our extended experience with gemfibrozil-lovastatin should provide additional useful information on the long-term safety and efficacy of what is becoming an increasingly more widespread pharmacologic practice, aggressive 2-drug management of high-risk hyperlipidemic patients who do not respond optimally to monotherapy.[3,6,14-19]

Follow-up visits on gemfibrozil-lovastatin therapy: Outpatient visits were scheduled every 6 to 8 weeks. After a 12-hour fast, at each visit, plasma lipids-lipopro-tein cholesterol levels were measured in our lipid research clinic's standardized laboratory,[23] liver function tests were performed, and at most visits creatine phosphokinase was measured. At each visit, an interval history was compiled, a brief physical examination was performed, and questions were systematically asked about myalgias, myositis and muscle tenderness. Major skeletal muscle groups were examined regularly at each visit for muscle tenderness. Patients were given a 24-hour phone number to our center, with instructions to call if muscle cramping, weakness or tenderness developed. Dietary adherence was emphasized by repeated visits with our dietitians, and by the use of a 7-day diet record for review of intake 1 week before the center visit.

To focus on the relationship of high creatine phosphokinase levels at baseline to high levels on follow-up, we separated the 6 and 61 patients having high and normal creatine phosphokinase at baseline (Table III). In 13 additional patients, having baseline liver function tests and lipid profiles, baseline creatine phosphokinase levels were not measured, but were subsequently obtained.

Statistical analysis: Because lipid-lipoprotein cholesterol levels were not normally distributed (Shapiro-Wilk test),[24] nonparametric paired Wilcoxon signed-rank tests were used to compare baseline and final values (Figures 1 to 4, 6 and 7). Mean values are displayed in Figures 1 to 4, 6 and 7; the significance values are from the Wilcoxon test.[24] One-way analysis of variance[24] was used to compare the percentage of high creatine phosphokinase levels in patients by lovastatin dose (Table II).

RESULTS

Patient characteristics at baseline: At baseline, despite the fact that 71 patients were taking 1-drug therapy (51 gemfibrozil, 20 lovastatin), and 4 more were receiving gemfibrozil-lovastatin, there was still severe mixed hyperlipidemia (Figures 1 to 4). At baseline, 77 of the 80 patients (96%) retained a total cholesterol/HDL cholesterol ratio >4.5/1, and had mixed hyperlipidemia (Figure 2). Moreover, 61% of the patients had low HDL cholesterol at baseline[13,14] (<35 mg/dl in men, <40 in women) (Figure 3), and also exhibited mixed hyperlipidemia. At baseline, 35% of the patients had high total cholesterol (>240 mg/dl) and triglycerides (>200 mg/dl) (Figure 4).

Of the 80 patients, 68% had already sustained atherosclerotic vascular disease; 48% had definite coronary heart disease, and 39% had cerebrovascular or occlusive peripheral vascular disease (Table I). Of the 80 patients, 49% had hypertension, 48% had low basal HDL cholesterol (<35 mg/dl[13]), 34% had a family history of premature definite coronary heart disease, and 24% smoked cigarettes (Table I). Aspirin or persantin was given to 40% of the patients, and antihypertensive drugs were given to 46% of patients (Table I). Thus, this was predominantly a secondary prevention study. The mode of the coronary heart disease risk factor score[13] distribution was very high, 3 risk factors; 90% of the patients had 2 to 7 risk factors (Table I).

TABLE I Clinical Characteristics of the 80 Patients

	% of Pts.
Definite coronary heart disease	48
Myocardial infarction	26
Angina	34
Arrhythmias	21
Angioplasty	5
Coronary artery bypass surgery	14
Definite coronary heart, or cerebrovascular, or peripheral vascular disease	68
Stroke	6
Transient cerebral ischemia	18
Carotid artery bypass	18
Claudication	23
Peripheral arterial bypass	4
Contributors to coronary heart disease risk	
Hypertension	49
Smoking	15
Diabetes	15
Severe obesity	20
Medications	
β Blocker	25
Diuretic	16
Calcium antagonist	24
ACE inhibitors	6
Enzyme inhibitor	
Oral hypoglycemic	11
Insulin	5
Hypouricemic	5
Aspirin or persantin	40
Antianginal	9
Antiarrhythmic	9
Coronary heart disease risk factors (13)	
Male sex	63
Family history of premature coronary heart disease (definite myocardial infarction or sudden death before age 55 years in a parent or sibling)	34
Cigarette smoking (currently smokes >10 cigarettes/day)	24
Hypertension	49
HDL cholesterol (<35 mg/dl)	48
Diabetes mellitus	15
History of definite cerebrovascular or occlusive peripheral vascular disease	39
Severe obesity (>30% overweight)	20

*Coronary heart disease risk factor score (13)

0	1	2	3	4	5	6	7	8

Number of patients by coronary heart disease risk factor score

(3)	(4)	(16)	(17)	(16)	(12)	(7)	(4)	(1)

ACE = angiotensin-converting enzyme; HDL = high-density lipoprotein.

Baseline and follow-up glucose, renal, liver, and creatine phosphokinase tests: For glucose, blood urea nitrogen, creatinine, liver function, and creatine phosphokinase tests, there were no significant changes (p >0.1) between the baseline and final visit with 2-drug therapy. Mean (SD) creatine phosphokinase at baseline (115 ± 64 U/liter) and at the final visit (109 ± 65 U/liter) in the 67 patients with baseline creatine phosphokinase measurements did not differ (p >0.1).

The 67 patients with measurements of baseline creatine phosphokinases had 603 batteries of 6 liver function tests during follow-up with 2-drug therapy (Table III). Of the liver function tests, 1.5% of total bilirubins were high, as were 3.2% of gamma glutamyl transferases, 4.3% of serum glutamic oxaloacetic transaminases, 8.0% of serum glutamate pyruvate transaminases, and 8.1% of alkaline phosphatases (Table III). Of the 3,618 follow-up liver function tests in these 67 patients, only 1 (0.03%), a gamma glutamyl transferase, was ≥3 times the upper normal limit, the cutpoint identified by the Food and Drug Administration guidelines as unacceptably high for patients taking lovastatin (Table III).

Of the 67 patients with a baseline creatine phosphokinase, 6 and 61 patients had high and normal levels, respectively, at baseline (Table III). Patients with high creatine phosphokinase at baseline were 8 times more likely (48 vs 6%) to have high levels on subsequent follow-up tests than those with normal levels at baseline (chi-square = 80, p <0.0001) (Table III). Of 576 creatine phosphokinase tests performed in the 67 patients with baseline creatine phosphokinase, 9% were above the laboratory upper normal limit for those taking 2-drug therapy, 3% were 1.5 times the upper normal limit, and 1 (0.2%) was ≥3 times the upper normal limit (Table III).

In the 13 patients without baseline creatine phosphokinase tests, with 138 batteries of 6 liver function tests and 138 creatine phosphokinase levels measured on follow-up, none of the liver function tests were ≥3 times the upper normal limit. Of the creatine phosphokinase levels, 7% were above the laboratory upper normal lim-

it, 4% were ≥1.5 times the upper normal limit, and none were ≥3 times the upper normal limit.

In all 80 patients, of the 714 creatine phosphokinase levels measured, 9% were elevated, only 3% were ≥1.5 times the upper normal limit, and 0.1% was ≥3 times the upper normal limit. Of 4,446 total liver function tests performed, only 5% were above the upper normal limit and 1 (0.02%) was ≥3 times the upper normal limit.

There were no significant differences in the percentage of high creatine phosphokinase levels per patient taking 2-drug therapy, when comparing dose levels in the groups taking lovastatin (p ≥0.7) (Table II).

Lipid-lowering effects of gemfibrozil-lovastatin therapy: After an average of 21 months of 2-drug therapy in the 80 patients, compared with baseline levels, mean total cholesterol decreased from 255 to 200 mg/dl (22%), LDL cholesterol decreased from 176 to 131 (26%), triglyceride levels decreased 35% from 236 to

TABLE II High Follow-Up Creatine Phosphokinase in 80 Patients Grouped by Lovastatin Dose at First and Final Visits on with Combined Therapy*

Lovastatin Dose (mg)	No. of Pts.	No. of Follow-Up Tests	Creatine Phosphokinase— %High Levels/Patient		
			X̄ ± SD	F	p Value
First Visit					
20	59†	471	6% ± 18		
40	14	171	2% ± 5		
60 or 80 (n=3) (n=4)	7	72	1% ± 3		
Total	80	714	5% ± 15	0.5	0.7
Final Visit					
20	39	311	6% ± 18		
40	27‡	268	4% ± 14		
60 or 80 (n=5) (n=9)	14	135	4% ± 12		
Total	80	714	5% ± 15	0.3	0.9

*Gemfibrozil 0.9 g, 1.2 g, 1.5 g taken by 1, 71 and 8 patients.
†Two patients starting therapy with 10 mg/day, 57 with 20 mg/day.
‡Two patients taking 30 mg/day, 25 taking 40 mg/day.

FIGURE 5. Distribution of the number of months of combined therapy with gemfibrozil and lovastatin in 80 patients with primary hyperlipoproteinemias, 67 with, 13 without baseline creatine phosphokinases.
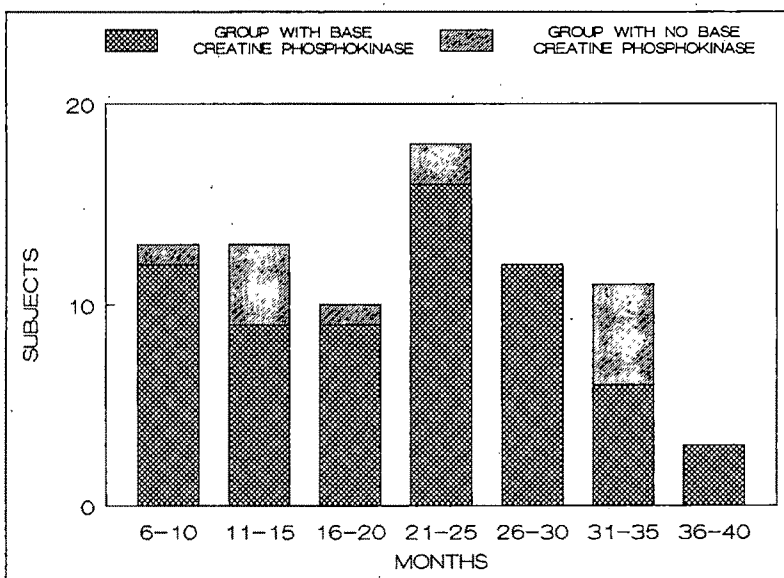
TABLE III Follow-up Liver Function and Creatine Phosphokinase Tests with Two-Drug Therapy in 67 Patients Taking Gemfibrozil-Lovastatin for a Minimum of Six Months

	Total High Values	Total Tests	% High Values	Values							≥1.5 × Upper Limit		≥3 × Upper Limit	
				1	2	3	4	5	6–9	≥10	n	%	n	%
GGT	19	603	3.2	2	1	0	1	0	0	1	7	1.2	1	0.2
SGOT	26	603	4.3	6	0	0	0	2	0	1	9	1.5	0	0
SGPT	48	603	8.0	7	2	0	1	0	1	2	8	1.3	0	0
Alkaline phosphatase	49	603	8.1	4	6	2	1	3	1	0	6	1.0	0	0
Total bilirubin	9	603	1.5	1	1	0	0	0	1	0	1	0.2	0	0
Direct bilirubin	0	603	0	0	0	0	0	0	0	0	0	0	0	0
All CK	53	576	9.2	11	4	1	0	3	2	0	16	2.8	1	0.2
Elevated CK at baseline (6 pts)	20	42	47.6	1	2	1	0	1	1	0	5	11.9	0	0
Normal CK at baseline (61 pts)	33	534	6.2	10	2	0	0	2	1	0	11	2.1	1	0.2

CK = creatine phosphokinase; GGT = gamma glutamyl transferase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase.

154, and the total chlesterol/HDL cholesterol ratio decreased from 7.1 to 5.4 (24%) (Figure 1). In the 77 patients with a baseline total cholesterol/HDL cholesterol ratio >4.5 and combined dyslipidemia, with 2-drug therapy mean total cholesterol decreased 23%, triglyceride decreased 35%, LDL cholesterol decreased 27%, and the total chlesterol/HDL cholesterol ratio decreased 25% (Figure 2). In the 49 patients with low baseline HDL cholesterol (<35 mg/dl in men and <40 mg/dl in women), with 2-drug therapy triglyceride levels decreased 39% and HDL cholesterol increased 16% from 32 (basal) to 37 mg/dl (final) (Figure 3). For the 28 patients with baseline total cholesterol >240 mg/dl and triglyceride levels >200 mg/dl, with 2-drug therapy total cholesterol decreased 30%, triglyceride levels decreased 57% from 317 to 137 mg/dl, HDL cholesterol increased 8%, LDL cholesterol decreased 32%, and the total cholesterol/HDL cholesterol ratio was reduced by 35% (Figure 4).

Of the 80 patients, 28 (35%) taking 2-drug therapy achieved both LDL (<130 mg/dl) and HDL (>35 mg/dl) cholesterol, with an 18% increase in HDL cholesterol (Figure 6). Of these 28 patients, the percentage taking lovastatin 20, 40 and 60 or 80 mg/day (53, 29 and 18%) did not differ from the 52 patients not achieving LDL cholesterol <130 mg/dl and HDL cholesterol >35 mg/dl (46, 37 and 17%, chi-square = 1.5, p >0.4). Of the 80 patients, 30% achieved a final total cholesterol/HDL cholesterol ratio <4.5 with a 26% increase in HDL cholesterol (Figure 7).
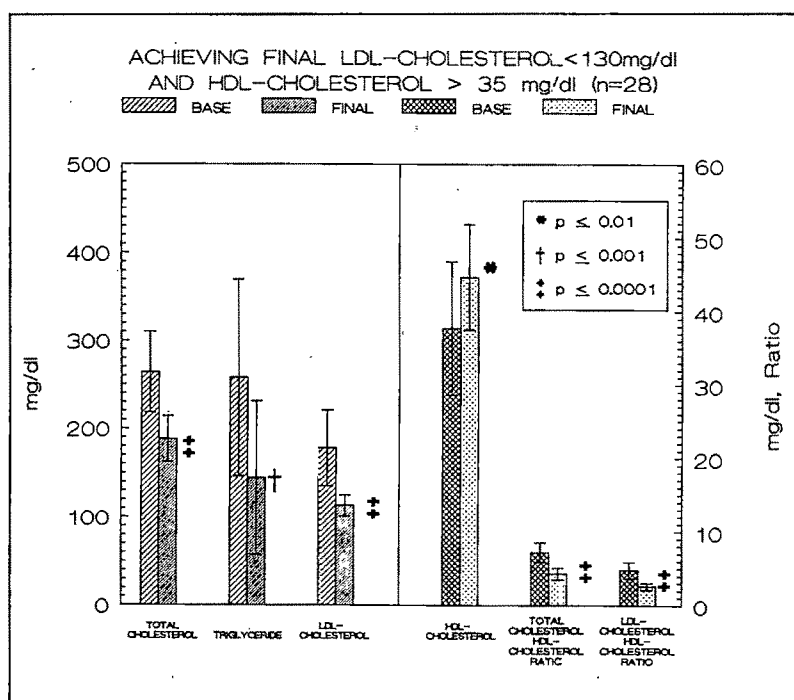
FIGURE 6. Mean (SD) baseline and (with gemfibrozil-lovastatin) final plasma total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (mg/dl), total cholesterol/HDL cholesterol ratio, and LDL/HDL cholesterol ratio in 28 patients achieving final LDL cholesterol <130 mg/dl and HDL cholesterol >35 mg/dl with 2-drug therapy.

Cessation of gemfibrozil-lovastatin attributable or not attributable to two-drug therapy: Overall, 92 patients in the cholesterol center had taken gemfibrozil-lovastatin, with 80 entered into the current study, having taken 2-drug therapy ≥6 months (Figure 5). Of the remaining 12 patients, 8 are still taking the 2-drug regimen, but have not (to date) taken 2-drug therapy for ≥6 months, and 4 patients stopped gemfibrozil-lovastatin before 6 months because of muscle symptoms.

In 3 of the 92 patients (3%), because of muscle symptoms or high creatine phosphokinase, or both, which were potentially attributable to the 2-drug therapy, gemfibrozil-lovastatin was discontinued. One of these 3 patients had a high creatine phosphokinase (769 U/liter). Five patients with symptomatic myalgias (with concurrent normal creatine phosphokinase levels) discontinued gemfibrozil-lovastatin for reasons not attributable to 2-drug therapy (lumbar and cervical disc syndromes, arthritis, diverticulitis). Of the 8 patients with symptoms leading to temporary or final cessation of 2-drug therapy, none had rhabdomyolysis, myoglobinuria or renal failure.

DISCUSSION

Myopathy including rhabdomyolysis, myoglobinuria and renal failure in patients receiving gemfibrozil-lovastatin (often with concomitant cyclosporine) has previously been reported.[21,22] However, although the numerator (incident case or cases) is known, the denominator, the number of patients receiving gemfibrozil-lovastatin from which these cases were taken, is not known.[21,22] When gemfibrozil-lovastatin therapy has been studied retrospectively[15] or prospectively,[16-19] in which both the numerator (incident cases) and denominator (number of patients receiving 2-drug therapy) are known, there have been few to no problems with myositis, and none

with rhabdomyolysis and renal injury. In our current study, myositis, symptomatic enough to discontinue 2-drug treatment, and attributable to gemfibrozil-lovastatin, occurred in 3% of patients, and in only 1% with concurrent high creatine phosphokinase (769 U/liter). No patient had rhabdomyolysis, myoglobinuria or renal failure.[21,22] Of those patients having high creatine phosphokinase at baseline with 1-drug therapy, 48% of follow-up levels with 2-drug therapy were high versus only 6% of high follow-up levels in patients with normal baseline creatine phosphokinase. This emphasizes the importance of knowing baseline creatine phosphokinase in the interpretation of elevated levels on follow-up.

In 80 patients, 9% of follow-up creatine phosphokinase levels were high, 3% were ≥1.5 times the upper normal limit, and only 0.1% were ≥3 times the upper normal limit. The finding of 9% high creatine phosphokinase levels with 2-drug therapy in the current study was very similar to that (11%) previously reported in 339 of our hyperlipidemic patients receiving no lipid-lowering drugs.[15] Of the 1,663 patients taking placebo for 48 weeks in the Expanded Clinical Evaluation of Lovastatin study, 29% had high creatine phosphokinase with or without muscle symptoms versus 29 and 35% of patients receiving 20 and 40 mg/day of lovastatin.[25]

In our clinical practice and in this study, gemfibrozil-lovastatin therapy was restricted to high-risk patients, 68% of whom had already sustained atherosclerotic vascular disease, with significant combined hyperlipidemia despite diet and monotherapy. Moreover, 49% of our patients had hypertension, 61% had high-risk, low HDL cholesterol, 34% had a family history of premature coronary heart disease and 24% smoked cigarettes. As in the current study, gemfibrozil-lovastatin therapy is best suited in high-risk patients with combined hyperlipidemias in whom monotherapy may

FIGURE 7. Mean (SD) baseline and (with gemfibrozil-lovastatin) final plasma total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (mg/dl), total cholesterol/HDL cholesterol ratio, and LDL/HDL cholesterol ratio in 24 patients achieving a final total cholesterol/HDL cholesterol ratio <4.5/1 with 2-drug therapy.

ACHIEVING FINAL TOTAL–CHOLESTEROL/
HDL–CHOLESTEROL RATIO < 4.5/1 (n=24)

* $p \leq 0.01$
† $p \leq 0.001$
‡ $p \leq 0.0001$
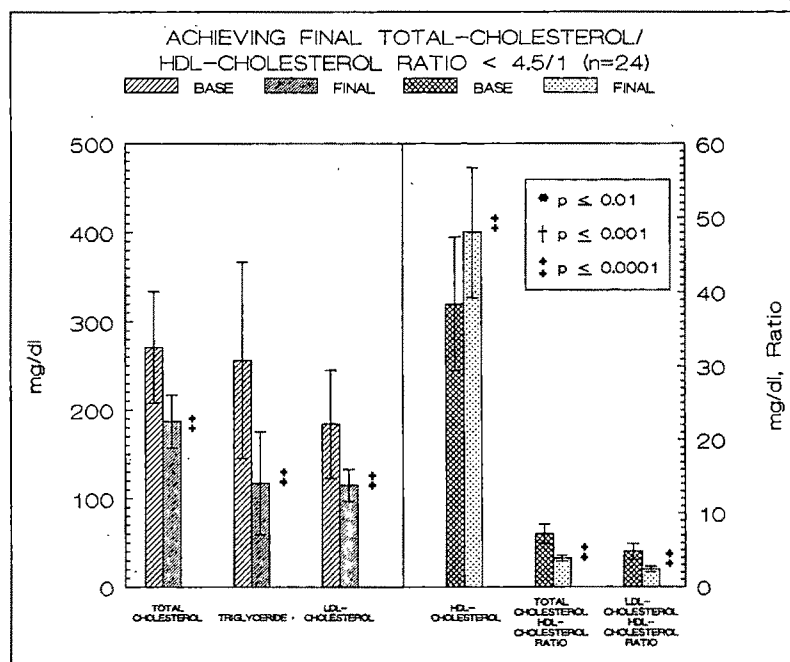
be insufficient.[15,16,18,19,26] Nicotinic acid-lovastatin increases the risk of rhabdomyolysis[20] and is a difficult combination to use because of nicotinic acid-mediated side effects[27] (flushing, itching, ulcerogenic, diabetogenic, raising uric acid, hepatotoxicity), often forcing cessation of 2-drug therapy. Because resins may worsen preexisting hypertriglyceridemia,[28] even in conjunction with nicotinic acid, this 2-drug combination may also not be optimal in treating combined hyperlipidemia. Resin-lovastatin, while potently lowering LDL cholesterol, may not elevate HDL cholesterol, and may raise triglycerides.[3,6] With careful surveillance, gemfibrozil-lovastatin can be given within reasonable safety boundaries[15,16-19] as in our current study, but a variety of 1-[19] or 2-drug therapies can also be used, optimized to each patient.

In the current study, in 80 patients who had not achieved optimal lipid-lipoprotein levels with diet and 1 drug, gemfibrozil-lovastatin reduced cholesterol 22%, triglyceride 35% and LDL cholesterol 26% beyond the effects of 1-drug therapy alone. This LDL cholesterol reduction was comparable to that induced by adding lovastatin to gemfibrozil reported by East et al.[16] Mean total and LDL cholesterol in our patients receiving 2-drug therapy, 200 and 131 mg/dl, approximated the values achieved in the Cholesterol Lowering Atherosclerosis and Familial Atherosclerosis Treatment studies[1,3] (on colestid-nicotinic acid), levels that led to stabilization and regression of coronary artery atherosclerosis in many patients.[1,3]

Particularly in men and women with low HDL cholesterol, <35 and <40 mg/dl (61% of our cohort), 1 drug alone often failed to raise HDL cholesterol >35 mg/dl, or to optimize the total cholesterol/HDL cholesterol ratio, whereas 2-drug therapy raised their mean HDL cholesterol from 32 to 37 mg/dl (16%) (p ≤0.0001), and decreased their total cholesterol/HDL cholesterol ratio 27% (p <0.0001).

Congruent with previous studies,[15,16-19] we found that gemfibrozil-lovastatin effectively modified lipoprotein levels, with infrequent myositis and without rhabdomyolysis, myoglobinuria or renal failure. We have seen 1 patient who had total cholesterol of 515 mg/dl and triglyceride level of 2,090 mg/dl; while receiving gemfibrozil 1.5 g/day and lovastatin 40 mg, severe thigh and leg muscle weakness developed, with creatine phosphokinase increasing from 357 to 31,251 U/liter and myoglobinuria (350 ng/ml) occurring without renal injury. Her myopathy resolved entirely over 10 days with return of creatine phosphokinase to normal (123 U/liter).

Preexisting renal insufficiency or concurrent use of cyclosporine, nicotinic acid or erythromycin, or a combination, sharply increases the likelihood of myopathy[20,29-32] well above the 0.5% reported for lovastatin alone.[33,34]

Because myopathy, rhabdomyolysis, myoglobinuria and renal injury have been reported in patients taking gemfibrozil-lovastatin,[21,22] those taking this combination should be carefully monitored every 6 to 8 weeks, with palpation of skeletal muscles, and serial measure-

ments of creatine phosphokinase and liver function. Gemfibrozil-lovastatin should be reserved, as in our center, predominantly for secondary prevention in high-risk, reliable patients with mixed hyperlipidemia who fail to respond optimally to 1-drug therapy, and who are well informed about the symptoms of possible myopathy. Patients should also have access to a 24-hour telephone "hot-line" to promptly report any muscle pain, tenderness or weakness, and should be instructed, if symptomatic, to discontinue 2-drug therapy pending further clinical evaluation.

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Comparison of Delay Times to Hospital Presentation for Physicians and Nonphysicians with Acute Myocardial Infarction

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To evaluate whether patients who recognize the symptoms of myocardial ischemia and have easy access to medical care have shortened time delays between onset of symptoms and hospital presentation, the total time interval between symptom onset and hospital arrival for 258 U.S. male physicians experiencing a first acute myocardial infarction (AMI) in the Physicians' Health Study (PHS) was compared with that of a comparable group of 240 men enrolled in the U.S. component of the Second International Study of Infarct Survival (ISIS-2), as well as with those of previously published series of patients with AMI. For patients presenting for medical care within 24 hours of symptom onset, the median time delay from onset of symptoms to presentation for medical care was 1.8 hours in the PHS, and 4.9 hours in the U.S. component of ISIS-2 (p <0.001). Furthermore, 56% of participants in the PHS presented for medical care within 2 hours and 72% within 4 hours of symptom onset compared with 20% (p <0.001) and 44% (p <0.001), respectively, for ISIS-2 participants. In previously published series, the average time to presentation was comparable to that in the ISIS-2 trial, with variation depending on country of origin and on local population density. The median time to medical presentation in any previous series was not shorter than that in the PHS. Thus, physicians in the PHS had significantly shorter time delays between onset of symptoms and presentation for medical care. This difference may help explain the far lower than expected cardiovascular mortality rates among physician participants in the PHS. Furthermore, the data provide encouraging evidence that shorter delay times from onset of symptoms to hospital presentation can be achieved.

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The time delay between onset of symptoms and hospital presentation is a critical factor in determining both short- and long-term mortality after acute myocardial infarction (AMI).[1-3] In general, approximately 50% of all cardiovascular deaths occur in the prehospital phase of AMI, a time period usually between 3 and 6 hours after onset of symptoms. It is during these early hours that lifesaving defibrillation,[4-6] as well as the initiation of therapies such as aspirin, β blockade and thrombolysis,[7-15] has been shown to be most effective. In recent years, it was suggested that reductions in 2 potentially modifiable factors — patient decision and transportation time — may lead to a shortening of the total delay between symptom onset and presentation for care.[2,3,16-23] Although patient education programs designed to reduce decision time, and specialized ambulance programs designed to reduce transportation time are generally believed to be useful,[24-26] little objective population-based data demonstrating the efficacy of these services are available. We hypothesized that a group of patients well-educated in the recognition of myocardial ischemic symptoms who also had easy and rapid access to medical facilities may have shorter total delay times to hospital presentation than those of the general population. On an a priori basis, physicians would appear to be 1 such patient group. Thus, in this analysis we compare the time delay to hospital presentation for physicians experiencing AMI in the Physicians' Health Study (PHS)[27] with that of a similar group of nonphysicians experiencing AMI in the U.S. component of the Second International Study of Infarct Survival (ISIS-2).[11]

METHODS

All patients with a first AMI in either the PHS or the U.S. component of ISIS-2 were screened for eligibility in this analysis. The PHS is a randomized, double-blind, placebo-controlled trial of aspirin and β-carotene in the primary prevention of cardiovascular disease and cancer among 22,071 U.S. physicians (aged 40 to 84 years) with no history of AMI, stroke or transient ischemic attacks.[27] Time delay between symptom onset and hospital presentation for AMI was obtained by reviewing the emergency room or attending physician notes from the time of admission. The ISIS-2 trial was an international, randomized, double-blind, placebo-controlled trial of aspirin or streptokinase, or both, in reducing cardiovascular mortality among 17,187 patients with suspected developing AMI presenting to the hospital within 24 hours of symptom onset.[11] The length of

time between symptom onset and hospital presentation was recorded at randomization for each participant.

To increase comparability between subjects enrolled in the PHS and ISIS-2, only those who met inclusion criteria for both trials were included in the current analysis. Thus, eligibility was restricted to U.S. men aged >40 years with no history of AMI, who had AMI between 1982 and 1988, and for whom time to presentation was known to be <24 hours. Of the 378 subjects with AMI in the PHS, 57 were ineligible for the current analysis because medical care was not obtained within 24 hours of symptom onset. An additional 63 subjects were excluded because they had an out-of-hospital cardiac death, reported an AMI without seeking hospitalization or had incomplete clinical data. Thus in all, 258 PHS participants (68.2%) who had AMI met the combined entry criteria. Similarly, of 407 subjects with AMI in the U.S. component of ISIS-2, 167 were excluded because they were women (n = 107) or had a prior AMI (n = 60). Thus, 240 ISIS-2 participants (59%) met the combined entry criteria.

Median delay time to presentation was calculated for each trial. The significance of differences in median time to presentation between the PHS and the U.S. component of ISIS-2 was tested using a median test statistic. Differences between the proportions of patients presenting within 2, 4 and 8 hours of onset of symptoms were tested by a chi-square statistic. All p values are 2-tailed.

As a second comparison group, we identified 16 studies that reported the median time interval between onset of symptoms and presentation for medical care among patients with AMI. Herlitz et al[3] previously summarized the available data that includes information from the Myocardial Infarction Community Registry[28] and the Metroprolol in Acute Myocardial Infarction trial,[8] as well as observational studies from Sweden,[29] Boston, Massachusetts,[16] Bethesda, Maryland,[17]

Rochester, Minnesota,[18] Palo Alto, California,[19] and Doncaster, United Kingdom.[20]

RESULTS

Figure 1 presents the distribution of time intervals between onset of symptoms and presentation for medical care for the 258 eligible male physicians with a first AMI in the PHS. Of these subjects, 144 (56%) presented within 2 hours of onset of symptoms. Specifically, 77 physicians (30%) presented within 1 hour, and 67 (26%) between 1 and 2 hours after onset of symptoms. Only 44 physicians included in this analysis (17%) presented for treatment between 8 and 24 hours after onset of symptoms.

The distribution of time to presentation in ISIS-2 is markedly different. Of 240 subjects with AMI, only 48 (20%) presented within 2 hours (Figure 2). Specifically, 13 subjects (5%) presented within 1 hour, and 35 (15%) between 1 and 2 hours. In ISIS-2, the largest percentage of patients presented between 4 and 8 hours, with 71 (30%) seeking medical care after 8 hours.

We calculated the median delay time for each study group (a measure of time delay minimally skewed by unusually early or late arrivers) to further compare these 2 distributions. The median time delay from onset of symptoms to presentation was 1.8 hours for participants in the PHS compared with 4.9 hours in ISIS-2 (p <0.001).

Because patients with AMI presenting within the first few hours of onset of symptoms may be more likely to receive certain therapies (in particular thrombolysis), we calculated for each trial the percentage of all subjects presenting within 2, 4 and 8 hours after onset of symptoms. Significantly higher proportions of participants presented in the PHS than in ISIS-2 at each of these time intervals (Figure 3).

With respect to previous studies, Figure 4 presents data comparing the median time from symptom onset
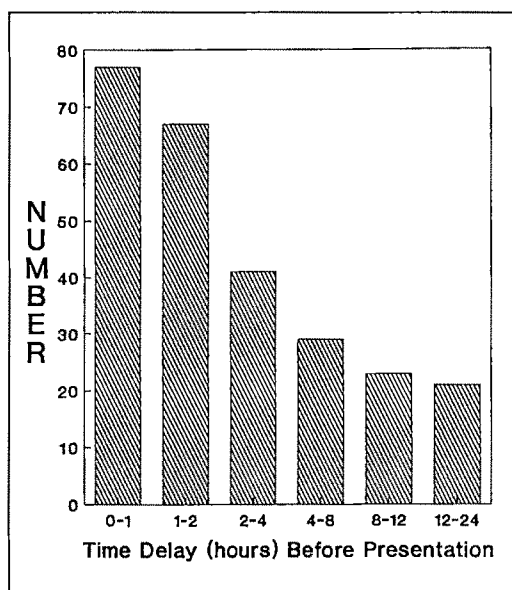
FIGURE 1. Distribution of time delay between onset of symptoms and treatment for 258 subjects with first myocardial infarction in Physicians' Health Study.
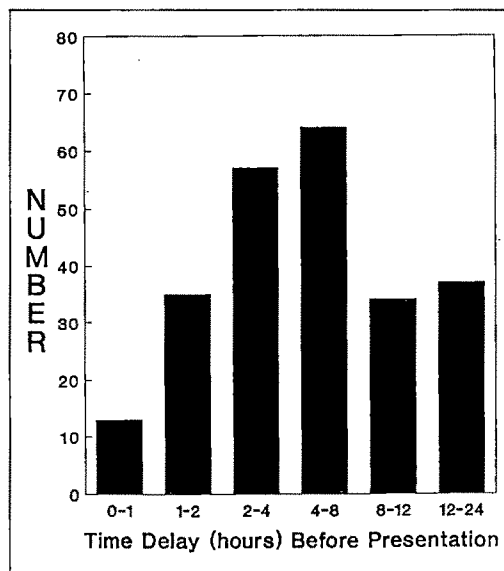
FIGURE 2. Distribution of time delay between onset of symptoms and treatment for 240 subjects with first myocardial infarction in U.S. component of Second International Study of Infarct Survival.

to hospital presentation in the PHS and the U.S. component of ISIS-2 with 16 other published series of AMI. These series (adapted from Herlitz et al)[3] reflect delay times in both urban and rural settings over a wide geographic distribution. Median delay times in these studies range from 2 to 8.5 hours, with the average time to presentation comparable to that seen in the U.S. component of ISIS-2. The median time to medical presentation was not shorter in any of these previous series than in the PHS.

DISCUSSION

The data indicate that physician participants in the PHS had significantly shortened delay times from onset of ischemic symptoms to hospital presentation compared with those of nonphysician participants in the U.S. component of ISIS-2. Specifically, in the PHS, >50% of all patients with a first AMI presented within 2 hours of symptom onset, whereas in ISIS-2, the comparable figure was 20%. For patients presenting within 24 hours of onset of symptoms, the median time to presentation in the PHS was significantly shorter than that in ISIS-2 (1.8 vs 4.9 hours; p <0.001). When compared with 16 previously published series, randomized doctors in the PHS again appear to have uniquely short median delay times, even though they presented to hospitals over a wide geographic territory that included both urban and rural settings. Thus, physician participants in the PHS had significantly shorter delay times between onset of symptoms and presentation for treatment than those of participants in ISIS-2 or the published literature.

Although inferences based on the observational data should be made with caution, it is interesting to speculate on the role shortened delay time to presentation may have had in the exceptionally low cardiovascular mortality rates seen in the PHS. It was anticipated at the beginning of the PHS that physicians participating in the trial, because of health consciousness as well as the healthy volunteer effect, would have a cardiovascular mortality rate only 40% of that of a general population of men of the same age. In fact, the cardiovascular mortality in the PHS was <15% of that of the general population.[27] This reduced rate could be due to a number of factors that lowered the incidence of acute ischemic events such as better health habits and higher socioeconomic status. For example, 11% of physician participants in the trial were current smokers compared with 29% of the U.S. population of men of the same age.[30] However, in addition to a reduced incidence rate, physician participants in the PHS had an unusually low case fatality rate; <10% of all AMIs in the study were fatal.[27] Thus it appears that factors in addition to those that reduced the incidence of disease are likely to have contributed to the overall low cardiovascular mortality rate.

Although it is tempting in this context to conclude that shortened delay time in the PHS may have had a role in reducing case fatality rates, differences between the PHS, ISIS-2 and each previously published study in terms of patient selection criteria and posthospitalization treatment strategies make it impossible to directly test this hypothesis. For example, despite early arrival, few participants in the PHS received thrombolytic therapy, whereas in ISIS-2, thrombolytic therapy was part of the randomization protocol. Furthermore, comparable data regarding AMI severity and revascularization rates are not available, precluding a survival analysis that controls for these important confounding variables.

Despite these limitations, several lines of indirect evidence support the possibility that shortened delay times observed in the PHS contributed to improved survival. First, several previous studies demonstrated that subjects presenting earlier for hospitalization have reduced short- and long-term mortality. For example, in the Multicenter Investigation of the Limitation of Infarct Size trial, a significantly higher mortality rate was observed in patients with AMI who arrived late for hospitalization, despite the fact that patients with hemodynamic compromise tended to arrive earlier.[1] Similarly,
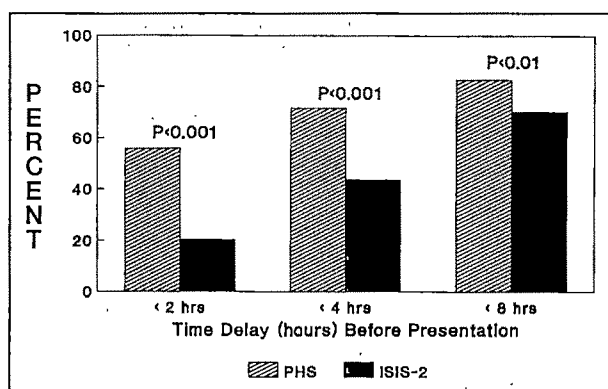
FIGURE 3. Percentage of subjects in Physicians' Health Study (PHS) and U.S. component of Second International Study of Infarct Survival (ISIS-2) presenting for medical care within 2, 4 and 8 hours of symptom onset.
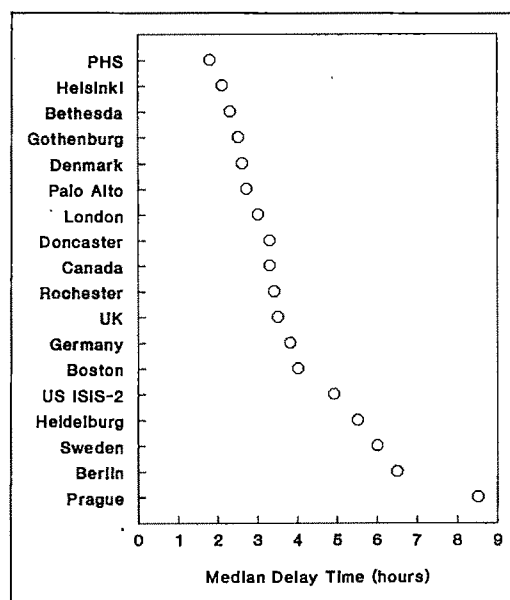
FIGURE 4. Median time delay between onset of symptoms and presentation for medical care in Physicians' Health Study (PHS), U.S. component of Second International Study of Infarct Survival (US ISIS-2), and 16 previously published studies.

Rawles and Haites[2] demonstrated that patients with acute ischemia delaying hospital admission between 4 and 8 hours had a mortality of 38%, or nearly twice that of early arrivers. Second, it has been demonstrated that the majority of deaths after AMI occur within hours of the onset of ischemia, and many are preventable by emergency cardioversion.[4-6] Finally, a growing series of large clinical trials has demonstrated that early aggressive medical intervention (particularly with aspirin, β-adrenergic blockers and thrombolytic therapy) can result in reduced case fatality rates for patients with AMI.[7,10-15,31]

Several factors influencing both decision and transportation time are likely to be responsible for the shortened total delay to hospitalization observed among physicians in this analysis. In addition to their medical education, physicians are more likely than the general public to work and live near a medical center, thus shortening the distance needed to travel after the onset of symptoms. For the general public (who are less likely to be near a hospital at the time of AMI) improvements in total delay time are most likely to be due to reductions in decision time. Media campaigns in Canada[32] and Sweden[33] demonstrated that public education programs can reduce patient decision time and perhaps shorten the total delay to hospital presentation.[24] Our data provide additional encouraging evidence that shorter delay times from onset of symptoms to presentation for treatment can be achieved, an important finding as programs designed to reduce total delay are being appraised.[23,25,26]

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Noninvasive Identification of Severe Coronary Artery Disease Using Exercise Tomographic Thallium-201 Imaging

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The ability of exercise thallium-201 tomographic imaging to predict the presence of left main or 3-vessel coronary artery disease (CAD) was examined in 688 patients who underwent both exercise thallium-201 testing and coronary angiography. Significant differences existed for multiple variables between patients with (n = 196) and without (n = 492) severe left main or 3-vessel CAD. Logistic regression analysis identified 4 variables as independently predictive of left main or 3-vessel CAD. These variables were the magnitude of ST-segment depression with exercise, the number of visually abnormal short-axis thallium-201 segments, the presence or absence of diabetes mellitus, and the change in systolic blood pressure with exercise. Using these variables, patients were classified by nomograms into low-, intermediate- and high-probability groups. Patients at high probability (n = 205) had a 52% prevalence of 3-vessel or left main CAD, whereas those at low probability (n = 170) had only a 12% prevalence. Only 53 patients (29%) with 3-vessel or left main CAD had perfusion abnormalities in all 3 coronary territories. Clinical and exercise parameters provide important independent information in the identification of left main or 3-vessel CAD by exercise thallium-201 tomographic imaging, because thallium scintigraphy alone is suggestive of extensive CAD in few patients.

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Prior studies showed exercise thallium imaging to have prognostic value independent of coronary anatomy.[1-6] In randomized trials revascularization has been shown to primarily have beneficial prognostic impact on left main or 3-vessel coronary artery disease (CAD).[7-10] Consequently, noninvasive identification of such patients can improve survival. Prior studies used exercise planar thallium imaging and radionuclide angiography to identify patients with 3-vessel or left main CAD.[11-16] The use of exercise tomographic thallium imaging has become widespread owing to its enhanced ability to localize CAD and to minimize overlap of structures compared with that of planar imaging.[17-21] Previous studies suggested that tomographic thallium exercise imaging is superior to planar imaging for the detection of 3-vessel or left main CAD.[17,20,21] However, these studies were retrospectively performed on small study groups, and focused on thallium scintigraphic data alone without considering clinical and exercise data. This study provides clinically useful noninvasive predictions of the likelihood of the presence of significant left main or 3-vessel CAD, using clinical, exercise and tomographic thallium imaging variables in a large patient cohort.

METHODS

Study patients: The study group consisted of a consecutive series of patients who underwent exercise thallium tomographic imaging between November 1986 and December 1989, and coronary angiography within 6 months of exercise testing. Patients were selected from 6,669 who underwent exercise thallium scintigraphy in our laboratory during this time period. Exclusion criteria included the following: (1) previous coronary revascularization by either coronary angioplasty or coronary artery bypass surgery, (2) left bundle branch block, ventricular preexcitation or a paced rhythm, and (3) hemodynamically significant valvular heart disease. In all, 688 patients (528 men and 160 women) were included in the study group. There were 286 patients with evidence of a prior myocardial infarction by history or the presence of significant Q waves on the electrocardiogram at rest.

Many patients (85%) were receiving antianginal medications at the time of exercise testing (233 β-receptor blockers, 257 long-acting nitrate preparations, and 359 calcium antagonists). There were 70 patients (10%) who received digitalis within 48 hours of exercise testing.

Multiple clinical variables (Table I) were prospectively collected for each patient. Hypercholesterolemia was defined as a total cholesterol level >250 mg/dl or chronic use of a cholesterol-reducing agent. Hypertension was defined as an increase in blood pressure >140/90 mm Hg for ≥6 months, or the chronic use of antihypertensive medication. Diabetes was defined as a fasting glucose level >140 mg/dl, or chronic use of insulin or oral hypoglycemic agents.

Exercise protocol: All patients underwent symptom-limited treadmill exercise using either the Bruce (n = 527) or Naughton (n = 161) protocol. For patients performing the Naughton protocol, a conversion factor was applied to equate exercise duration with the Bruce protocol.[22] Heart rate, blood pressure by cuff sphygmomanometry, and 12-lead electrocardiograms were obtained at 1-minute intervals. ST-segment displacement was measured 80 ms after the J point and classified as <1, 1 to 1.9 or ≥2 mm depression. At peak exercise, 4 mCi of thallium-201 were injected intravenously, and patients exercised an additional minute.

Tomographic thallium-201 imaging: Patients were imaged in the supine position 10 minutes after the termination of exercise, and 4 hours later using a large field-of-view, single-crystal, rotating gamma camera (Elscint 409) equipped with an all-purpose, parallel hole collimator. A single planar anterior image was obtained for 5 minutes (with a 20% energy window centered on the 70 to 80 KeV x-ray peak of thallium-201, and a second window centered at 170 KeV) to assess cardiac size and pulmonary activity. Tomographic imaging was then performed over a 180° arc from 45° right anterior oblique to 45° left posterior oblique, using a step and shoot method. In all, 30 images were obtained at 6° intervals for 40 seconds each. Each projection was corrected for nonuniformity with a 30 million count flood from a cobalt-57 source. Filtered back projection was performed with a Ramp-Hanning filter, with a threshold value of 0.5 cycles/pixel. Axial filtration was performed perpendicular to the slice. Orthogonal images were generated by oblique angle reconstruction producing horizontal long- and short-axis, and vertical long-axis slices that were each 6 mm thick.

Visual analysis of tomographic images: Visual assessment of thallium tomographic images was performed by consensus of 2 experienced observers. Cardiac enlargement and pulmonary uptake were assessed subjectively as present or absent. Pulmonary uptake was visually assessed in all cases and quantitated in borderline cases by the ratio of maximal pulmonary/myocardial counts (values >0.5 were considered increased). Short-axis images were divided in 14 segments (as previously described by the Mayo Clinic) corresponding to the septal, anterior, lateral and inferior walls at the apex, base and midventricle.[23] At the midventricle and basal levels, the septum was divided into anterior and inferior septums. A 5-point scoring system was used to assess each segment (4 = normal perfusion; 3 = mild hypoperfusion; 2 = moderate hypoperfusion; 1 = severe hypoperfusion; and 0 = no perfusion). A reversible defect was considered present if the delayed image demon-

TABLE I Variables

Clinical variables
  Age
  Gender
  Smoking history
  Family history of coronary artery disease
  Hypercholesterolemia
  Hypertension
  History of myocardial infarction
  Diabetes
Exercise variables
  Chest pain with exercise
  Dyspnea with exercise
  Peak heart rate
  Peak heart rate × systolic blood pressure
  Change in systolic blood pressure (peak to rest)
  Magnitude of ST depression
  METs achieved
Thallium variables
  Cardiac enlargement
  Increased pulmonary uptake
  No. of abnormal thallium segments; postexercise, 4 hours delayed, and (postexercise − delayed)
  No. of abnormal coronary distributions; postexercise, 4 hours delayed, and (postexercise − delayed)

strated ≥1 grade improvement in perfusion in any segment. A fixed defect was considered present if the degree of hypoperfusion was at least moderate (≤2) and equal on the postexercise and delayed images.

Short-axis segments were then assigned to the 3 coronary distributions. The left anterior descending distribution included the anterior and anteroseptal segments. The right coronary artery included the inferior and inferoseptal segments, and the left circumflex artery included the lateral segments. Because the vascular supply of the apex is variable, these 4 segments were not included in the coronary distributions. A coronary distribution was considered abnormal if a reversible or fixed defect was present in the corresponding short-axis segment and was confirmed as present in the appropriate region on either the vertical (anterior and inferior walls) or horizontal (septal and lateral walls) long axis.

Coronary angiography: All patients underwent coronary angiography ± 6 months from thallium exercise testing (2 ± 34 days). No patient had myocardial infarction in this interval. Coronary artery narrowing was visually estimated and expressed as percent luminal diameter stenosis. A 70% narrowing of the internal diameter of the left anterior descending, left circumflex and right coronary arteries or their major branches, and 50% narrowing of the left main coronary artery was considered significant.[7]

Statistics: An unpaired t or Pearson chi-square test was used to identify variables significantly associated with 3-vessel or left main CAD. A logistic regression analysis[24] was used to develop a multivariable model for predicting presence or absence of significant left main or 3-vessel CAD. Multiple clinical, and exercise electrocardiographic and thallium variables were considered for stepwise inclusion in the model (Table I). Variables were entered in the model until a simultaneous test of all the variables not yet entered was no longer signifi-

TABLE II Clinical, Exercise and Thallium-201 Variables Significantly Associated with Three-Vessel or Left Main Coronary Artery Disease

	Left Main or 3-Vessel Disease		
Variable	Present (n = 196)	Absent (n = 492)	p Value
Clinical			
Age (yr)	64 ± 9	62 ± 10	<0.05
Diabetes mellitus (%)	27	14	<0.001
Hypertension (%) (>140/90 mm Hg)	57	46	<0.01
Exercise			
Duration (METs)	6.9 ± 2.2	7.3 ± 2.3	<0.02
Magnitude of ST depression	1.5 ± 1.6	0.9 ± 1.3	<0.0001
Peak exercise heart rate (beats/min)	121 ± 24	126 ± 25	<0.01
Change in systolic blood pressure (mm Hg)	22 ± 31	35 ± 24	<0.0001
Exercise systolic blood pressure × heart rate	19,351 ± 6,290	21,501 ± 6,454	0.0001
Thallium-201			
Cardiac enlargement (%)	40	26	<0.001
Increased pulmonary uptake (%)	27	19	<0.05
No. of abnormal segments			
Postexercise	7.2 ± 3.9	5.2 ± 3.8	<0.0001
Delayed	4.4 ± 3.4	3.2 ± 3.4	<0.0001
Postexercise − delayed	2.8 ± 2.8	2.0 ± 2.4	0.0001
Abnormal coronary distributions			
Postexercise	1.9 ± 0.9	1.4 ± 0.9	0.0001
Delayed	1.2 ± 0.8	0.9 ± 0.8	0.0009
Postexercise − delayed	0.7 ± 0.8	0.5 ± 0.7	0.009

TABLE III Thallium-201 Tomographic Analysis

	Number of Vessels Diseased			
Variable	3 (n = 181)	2 (n = 227)*	1 (n = 170)	0 (n = 110)
Reversible segments†	90%	81%	77%	67%
Fixed segments only	6%	11%	8%	6%
≥1 abnormal segment	96%	92%	85%	73%
≥1 abnormal coronary distribution	93%	90%	84%	63%
3 normal coronary distributions	29%	21%	10%	5%

*15 patients with 2-vessel disease had significant left main disease.
†Includes patients with reversible or reversible and fixed abnormal segments.

cant at the p <0.05 level. This strict definition for model entry was used to prevent the detection of spurious associations with the presence or absence of significant left main or 3-vessel CAD, because of the multiple variables considered. The logistic regression model was then used to estimate the probability of left main or 3-vessel CAD for each patient by classifying them as low (<15%), intermediate (15 to 35%) or high (>35%) probability. These probability percentiles were chosen to correspond to those of a previous study from this laboratory using exercise radionuclide angiography.[16]

RESULTS

There were 688 patients in the study group; 196 (28%) had left main or 3-vessel CAD. Significant left main disease was present in 59 patients (9%). There were 110 patients (16%) who had no significant CAD,

170 (25%) who had 1-vessel CAD, and 227 (33%) who had 2-vessel CAD; 15 with 2-vessel CAD had significant left main CAD.

There were significant differences in multiple clinical, exercise and thallium variables between patients with and without 3-vessel or left main CAD (Table II). Patients with 3-vessel or left main CAD were older and had a higher prevalence of diabetes and hypertension. During exercise, patients with severe disease had a shorter exercise duration, greater magnitude of ST depression, lower peak heart rate, smaller increase in systolic blood pressure, and lower peak rate-pressure product. Patients with 3-vessel or left main CAD had a higher prevalence of cardiac enlargement, abnormal pulmonary uptake, and more abnormal thallium tomographic short-axis segments and coronary distributions on both postexercise and delayed imaging, as well as a greater change in abnormal segments between the 2 images (reflecting redistribution) than did those without such disease. In patients with 3-vessel or left main CAD (n = 196), the right coronary artery thallium distribution was most frequently abnormal (87%), followed by the left anterior descending territory (58%) and finally the left circumflex territory (47%).

Thallium-201 scintigraphy showed high sensitivity in detecting patients with CAD, but was not specific in this selected patient population (Table III). Most patients had reversible thallium defects after exercise; a minority had fixed defects alone. The finding of 3 abnormal coronary distributions in patients with 3-vessel CAD was infrequent (29%).

The logistic regression model identified 4 variables as independently predictive of the presence of 3-vessel or left main CAD. The most important variable was

the magnitude of exercise-induced ST depression (chi-square 16.6; p <0.0001), followed by the number of abnormal thallium segments on the poststress images (chi-square 17.5; p <0.0001), the presence of diabetes (chi-square 11; p = 0.0009), and the change in systolic blood pressure (peak − rest systolic blood pressure; chi-square 14.7; p = 0.0001). The chi-square for the model was 84.7. When patients receiving a β-receptor blocker were excluded, logistic regression analysis identified 3 of the same variables as independently associated with severe CAD (change in systolic blood pressure, number of postexercise abnormal thallium segments, and magnitude of ST depression). The chi-square of this model of 455 patients was 45.3. Diabetes was the next most sig-

nificant variable, but, in this subgroup, did not meet the strict entry criterion used for inclusion.

Prediction of low-, intermediate- and high-probability groups: The predicted probabilities were used to define low-, intermediate- and high-probability patient groups. Patients classified as low probability (n = 170) had a 12% prevalence (n = 21) of 3-vessel or left main CAD, whereas those classified as high probability (n = 105) had a 52% prevalence (n = 106). Patients with an intermediate probability (n = 313) had a 22% prevalence (n = 69) of 3-vessel or left main CAD. When patients who had relatively mild symptoms (angina ≤ New York Heart Association class II, and atypical or noncardiac chest pain) were analyzed (n = 444), the
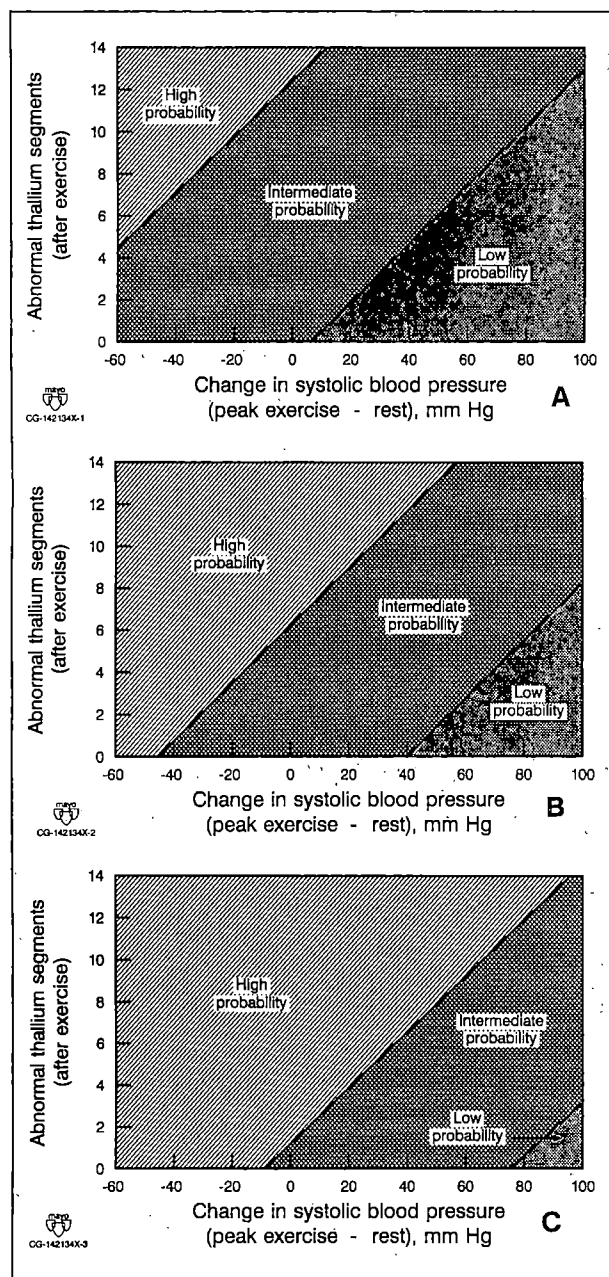
FIGURE 1. Estimated probability of left main or 3-vessel coronary artery disease for nondiabetic patients with ST-segment depression of *(A)* <1, *(B)* 1 to 1.9 and *(C)* ≥2 mm. *Zones* of different probabilities are shown.
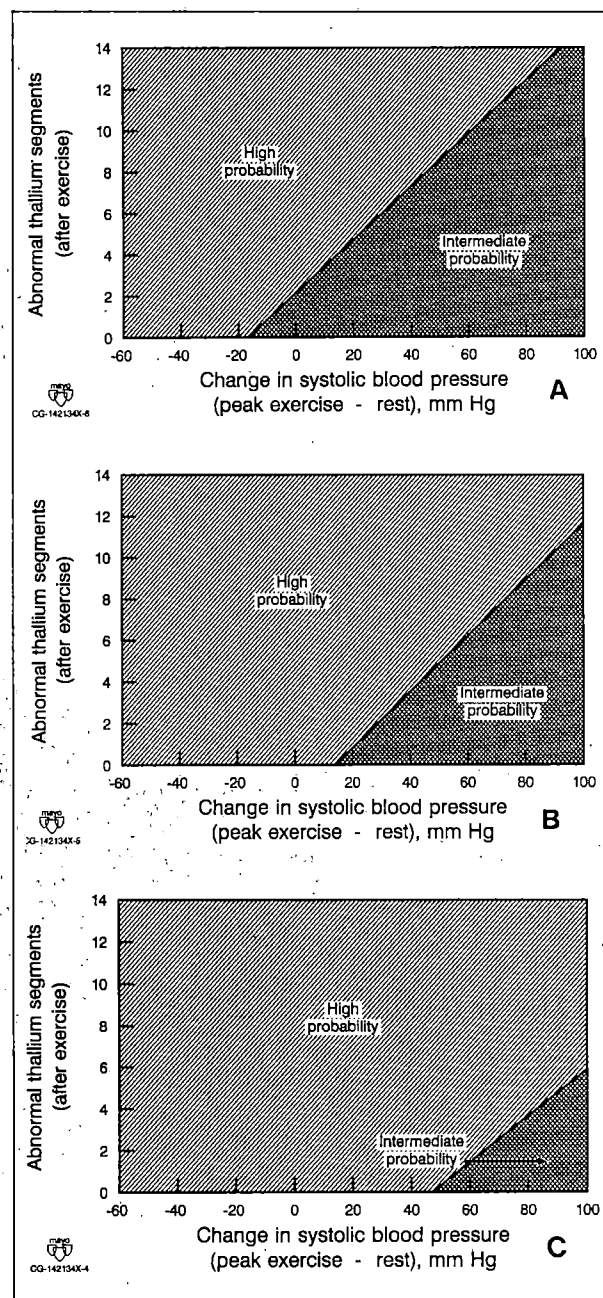
FIGURE 2. Estimated probability of left main or 3-vessel coronary artery disease for diabetic patients with ST-segment depression of *(A)* <1, *(B)* 1 to 1.9 and *(C)* ≥2 mm.

model performed similarly. Patients classified as low probability (n = 103) had a 14% prevalence (n = 14) of 3-vessel or left main CAD. Patients at intermediate risk (n = 231) had an 18% prevalence (n = 41) and those predicted to be at high risk (n = 110) had a 42% prevalence (n = 46) of 3-vessel or left main CAD.

These variables (magnitude of ST depression with exercise, number of postexercise abnormal thallium segments, diabetes and change in systolic blood pressure with exercise) were then used in nomograms to provide a practical estimate of the risk of 3-vessel or left main CAD. The results for nondiabetic patients for a given degree of ST-segment depression are shown in Figure 1. Each panel displays the probability of left main or 3-vessel CAD as a function of the number of abnormal postexercise short-axis tomographic thallium segments, and the change in systolic blood pressure. For example, a nondiabetic patient with <1 mm ST depression and an increase in systolic blood pressure of 30 mm Hg was at low risk if there were ≤3 abnormal thallium segments and at intermediate risk if there were >3 abnormal segments. The probability of 3-vessel or left main CAD for diabetics, using the same variables, is shown in Figure 2. For example, a diabetic patient with ≥1 mm ST depression is at high risk if there are >3 abnormal segments with an increase in systolic blood pressure of <40 mm Hg. Patients with diabetes were never classified in the low-risk group, despite exercise and thallium data, and diabetics with ≥2 mm ST depression during exercise were predominantly classified in the high-probability group, with thallium scintigraphy providing limited clinical impact.

DISCUSSION

With the increasing use of tomographic thallium exercise testing, there is a need to provide practical estimates of the likelihood of severe CAD. These results demonstrate that there are multiple clinical, exercise and thallium imaging variables that are significantly different between patients with and without 3-vessel or left main CAD. Each variable is potentially useful for identifying patients with severe CAD.

Using the logistic regression model in a stepwise fashion, only 4 variables were identified that were independently predictive of 3-vessel or left main CAD (magnitude of ST depression, number of abnormal thallium segments after exercise, presence of diabetes, and change in blood pressure with exercise). Prior reports clearly established the importance of the magnitude of electrocardiographic ST change with exercise.[13,16,25,26] The total number of abnormal thallium short-axis segments obtained after exercise (14 maximum) rather than the number of abnormal coronary territories was also independently predictive of 3-vessel or left main CAD. The inclusion of the apical segments in this method of analysis may account for its superiority to abnormal coronary distributions, because it may more closely reflect the total ischemic burden of the left ventricle. Mahmarian et al[27] described the importance of the extent of total perfusion defect using tomographic exercise thallium imaging for discriminating 2- or 3-vessel from 1-vessel disease or absence of CAD. The association of

diabetes with extensive CAD has been well-described.[28] The change in systolic blood pressure with exercise, particularly a decrease in systolic blood pressure, was consistently associated with significant left main or 3-vessel CAD in previous studies and reflects significant ischemic exercise-induced myocardial dysfunction.[13,16,29]

Increased pulmonary uptake (which was previously associated with more extensive CAD) was significantly associated on a univariate basis with 3-vessel and left main CAD, but did not add further information on multivariate analysis.[30] This finding is likely due to the significant association between pulmonary uptake and the number of postexercise abnormal thallium segments (p <0.0001), and to the change in systolic blood pressure (p <0.0001), both of which indirectly reflect exercise-induced mechanical dysfunction of the left ventricle. The inability of pulmonary uptake to provide additional independent information for tomographic data was also reported by Kahn et al[31] and predicted by Diamond.[32]

Only a minority of patients with 3-vessel or left main CAD had all 3 coronary territories identified as abnormal. This may reflect our stringent criteria for thallium abnormalities. Breast and diaphragmatic attenuation can frequently cause mild fixed perfusion defects, and therefore, only moderate fixed defects (≤grade 2) were defined as abnormal. We also needed confirmation of abnormal segments on corresponding vertical and horizontal long-axis views in assessing perfusion for a coronary distribution. Furthermore, thallium-201 scintigraphy is a relative perfusion technique and may underestimate the number of diseased vessels in multivessel CAD.

Comparison with previous studies: Tamaki et al[33] reported that tomographic thallium imaging alone has a high sensitivity for the detection of abnormal vessels (67% by visual and 85% by quantitative analysis) in 20 patients with 3-vessel CAD. However, they did not report how many patients had all 3 coronary territories identified as abnormal by either technique. Mahmarian et al[27] in a larger patient population (n = 360) reported a high sensitivity of thallium tomographic imaging alone in the detection of multivessel CAD (visual 70% and quantitative 76%), but did not distinguish between patients with 2- and 3-vessel CAD.[27]

The results of this study with tomographic thallium imaging confirm those of Maddahi et al[3] who demonstrated the independent importance of exercise and planar thallium data in the detection of patients with 3-vessel or left main CAD. However, in the present study using tomographic imaging, we did not find as high a post-test likelihood for the presence of 3-vessel or left main CAD.[13] In the study of Maddahi et al, a disproportionate number of patients had 3-vessel or left main CAD (53%), whereas only 14% had normal coronary arteriograms, which may contribute to the high sensitivity and specificity. The present study has a more homogenous distribution of coronary disease (28% of patients with left main and 3-vessel CAD). Furthermore, we used multiple regression analysis in a large population to predict the likelihood of 3-vessel or left main CAD, using thallium scintigraphic parameters as con-

tinuous variables, rather than using multiple individual variables dichotomized as normal or abnormal.

The results of this study are similar to those reported in a previous study from this laboratory, using exercise radionuclude angiography.[16] In that study, magnitude of ST depression, exercise heart rate $\times$ systolic blood pressure product, exercise ejection fraction and gender provided the majority of predictive power of a logistic regression model in which 56% of patients classified as high probability (>0.35) had 3-vessel or left main CAD. Patients classified as low probability (<0.15) had a 9% prevalence of 3-vessel or left main CAD.

Clinical implications: The decision to proceed with coronary angiography is highly individualized, and the indications may be expanding with the widespread use of coronary angioplasty. Patients estimated to be at high probability should undergo early coronary angiography despite mild symptoms. The strong association of diabetes with extensive CAD found in this study is particularly significant; our results suggest that ST-segment depression in a diabetic patient is usually associated with a high probability of severe disease.

Study limitations: The foremost limitation in this study is the influence of referral bias, because all patients underwent coronary angiography, and that decision was likely influenced by the results of the thallium exercise test.[34] Specificity may have been significantly greater, and sensitivity somewhat lower, if the coronary anatomy was known in the 5,981 patients who were not referred for coronary angiography.

The presence of cardiac enlargement was evaluated in the present study, but transient ischemic dilatation, a marker of severe myocardial ischemia, was not.[35] Furthermore, pulmonary uptake was not systematically quantitated for all 688 patients. Finally, most patients were receiving antianginal medications at the time of exercise testing, which may affect the sensitivity of detecting significant perfusion abnormalities.

The other major limitation is the absence of quantitative interpretation of the thallium images. However, in the only other large study to date, Mahmarian et al[27] found the sensitivity of visual interpretation of thallium tomographic images equal to that of quantitative interpretation for the presence or absence of CAD. Prediction of multivessel CAD by visual and quantitative interpretation was also comparable in that study (70 vs 76%). The images in the present study were interpreted by 2 experienced observers. Thus, the addition of quantitative interpretation may not necessarily improve these results. However, qualitative interpretation may vary between institutions, and therefore, these results may not be applicable to some laboratories. Future prospective studies are needed to assess the added value of quantitation for the detection of 3-vessel and left main CAD.

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Effect of Thrombolytic Therapy on the Predictive Value of Signal-Averaged Electrocardiography After Acute Myocardial Infarction

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Standard time domain variables from signal-averaged electrocardiography were examined in a population of 331 survivors of acute myocardial infarction. Of these subjects, 130 received early (<24 hours) thrombolytic therapy. During a follow-up of ≥10 months, there were 17 arrhythmic events (8.5%) (sudden death or sustained symptomatic ventricular tachycardia) in the group without thrombolysis and 8 (6.2%) in those with thrombolysis. Statistically, highly significant differences between the signal-averaged electrocardiographic variables of patients with and without arrhythmic events were found in the group without thrombolysis, whereas only root-mean-square voltage of the terminal 40 ms of the signal-averaged QRS complex was statistically associated with outcome (the differences in the other 2 indexes being not significant) in patients with thrombolysis. When using 2 previously published categoric criteria for the diagnosis of abnormal signal-averaged electrocardiography, the performance of these criteria in predicting arrhythmic events was substantially better in the group without thrombolysis than in those with thrombolysis (positive predictive accuracy >3 times lower). Retrospectively adjusted receiver-operator characteristics showed that for a sensitivity of 30%, the maximum achievable positive predictive accuracy of signal-averaged electrocardiography for arrhythmic events was 100% in the group without thrombolysis, but only 27% in those with thrombolysis. It is concluded that standard signal-averaged electrocardiography after acute myocardial infarction is less informative in patients who receive thrombolytic treatment.

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The value of signal-averaged electrocardiography for the prediction of arrhythmic complications after acute myocardial infarction (AMI) has been clearly established.[1–7] The presence of late potentials is an important risk stratification factor, but the effect of therapeutic interventions on the diagnosis of late potentials and on their predictive value should be considered. This particularly applies to thrombolytic therapy, and several studies already showed the effects of thrombolysis on the incidence of late potentials in patients after AMI.[8–12] With the now frequent use of thrombolytic therapy in AMI, it has been suggested that the categoric criteria for risk stratification after AMI may need modification.[13] The effect of thrombolysis on the predictive value of late potentials recorded on signal-averaged electrocardiography has not been established. This study compares the value of signal-averaged electrocardiographic late potentials for the prediction of serious arrhythmic events in patients who did and did not receive early thrombolytic therapy during AMI.

METHODS

Patients: We examined 331 patients (aged 29 to 74 years) who were admitted to the hospital with AMI during the period of 1986 to 1990 for whom signal-averaged electrocardiography was available and who survived to discharge. AMI was diagnosed using previously described standard criteria.[14] Patients were excluded if they had noncardiac disease likely to increase mortality, important nonischemic cardiac disease, history of cardiac surgery, or permanent pacemaker insertion, or if they were aged >75 years or were unable to be followed up. Patients with bundle branch block or ventricular preexcitation were excluded, because the wide QRS patterns disturb the time domain signal-averaged electrocardiographic analysis. History of AMI was present in 39 patients who were included.

Patients were followed up for ≥6 months (mean 20) during which 32 died; 12 died suddenly (according to the Cardiac Arrhythmia Pilot Study definition),[15] and 13 had spontaneous sustained ventricular tachycardia.

Thrombolytic therapy: Beginning in the second half of 1988, eligible patients were given thrombolytic therapy. In the absence of contraindications, 1.5 million units of streptokinase were administrated to patients seen within 24 hours of the onset of major symptoms. Contraindications were active bleeding or history of coagulopathy, suspected aortic dissection, recent head injury (<3 months), documented proliferative diabetic retinopathy, fractured ribs secondary to traumatic resuscita-

TABLE I Characteristics of Patient Population

Pt. Group	No TT	TT Early	TT Late	Total
No.	201	100	30	331
Mean age (yr)	58	56	55	57
Women	41	19	8	68
Anterior AMI	104	53	8	165
Q-wave AMI	128	75	21	224

Characteristics of patients are shown for those receiving no thrombolytic therapy (TT), and for those receiving it ≤6 (Early) and >6 (Late) hours after onset of symptoms.
AMI = acute myocardial infarction.

TABLE II Numbers of Patients in Individual Groups

Pt. Group	VT	SD	Others	Total
No thrombolysis	8	9	184	201
Thrombolysis	5	3	122	130
All pts.	13	12	306	331

SD = sudden death; VT = sustained symptomatic ventricular tachycardia.

tion, systolic blood pressure <85 mm Hg or history of sensitivity to streptokinase. Streptokinase was also not used if it was previously administered within 5 to 365 days. Thrombolytic therapy was used in 130 patients of the study population.

Signal-averaged electrocardiography: A signal-averaged electrocardiographic record was obtained before discharge (day 5 to 11 after AMI) in each patient. Recordings were obtained on the Arrhythmia Research Technology system (model 1200 EPX), using Frank orthogonal leads and a sampling rate of 1 kHz. In each patient, 200 to 500 ventricular complexes were averaged; the achieved noise level was ≤0.5 μv. The analysis was performed with filter settings of 25 to 250 Hz, and the following standard quantitative variables were computed in each case: root-mean-square voltage of the terminal 40 ms of the signal-averaged QRS complex (RMS-40), total duration of the signal-averaged QRS complex (tQRS), and duration of low-amplitude signals <40 μv (LAS).

Several patients (n = 100) were treated with β blockers, but in all cases, signal-averaged electrocardiography was performed when the patient was receiving no other antiarrhythmic therapy.

Left ventricular ejection fraction: Before discharge from the hospital, patients performed a symptom-limited treadmill exercise test, using a Bruce protocol. Depending on the result of this test, left ventricular ejection fraction was obtained from either coronary angiography with left ventricular angiography or radionuclide angiography, using previously published techniques.[16]

Statistics and data manipulation: Because the incidence of late potentials has been shown to be associated with arrhythmic death or ventricular tachycardia,[1-7] the follow-up end point considered in this study was an arrhythmic event defined as either sudden cardiac death or symptomatic sustained ventricular tachycardia.

VALUES OF SIGNAL-AVERAGED ELECTROCARDIOGRAPHIC VARIABLES: The numeric values of individual signal-averaged electrocardiographic quantitative variables were compared for patients with and without arrhythmic

events. This comparison was performed for the total population and separately for groups of patients who did and did not receive thrombolytic therapy. The nonparametric Mann-Whitney U test was used for this purpose.

CATEGORIC CRITERIA FOR SIGNAL-AVERAGED ELECTROCARDIOGRAPHIC DIAGNOSIS: The signal-averaged electrocardiographic recording of each patient was classified as normal or abnormal, and the association of this diagnosis with the arrhythmic events was examined using Fisher's exact test. This examination was again performed for the total population and separately for subgroups of patients who did and did not receive thrombolytic therapy.

This whole procedure was performed twice, using 2 previously published criteria for the abnormality of signal-averaged electrocardiography: (1) tQRS ≤114 ms; LAS ≤38 ms; and RMS-40 ≥20 μv[17]; and (2) tQRS ≤120 ms; LAS ≤40 ms; and RMS-40 ≥25 μv.[6] With both criteria, the result was categorized abnormal if any 2 of the 3 variables had an abnormal value, and the incidence of abnormal signal-averaged electrocardiographic findings in the groups with and without thrombolysis was compared using Fisher's exact test.

STRATIFICATION OF ARRHYTHMIC EVENTS: The so-called receiver-operator characteristic curves that associate specificity with sensitivity were computed for the multivariate prediction of arrhythmic events, using all 3 signal-averaged electrocardiographic variables. For the computation of these curves, the dichotomy points of individual signal-averaged electrocardiographic variables were varied to achieve all possible values of sensitivity, and for each of these values, the maximum specificity was computed using a previously published algorithm.[18] The computation of receiver-operator characteristic curves was performed for the prediction of arrhythmic events in the total population and in the 2 subgroups (thrombolytic therapy used and not used). In all cases, ≥2 signal-averaged electrocardiographic variables were needed to exceed their dichotomy points for a positive result.

The same methods were used to compute the curves expressing the dependence of the maximum achievable positive predictive accuracy on sensitivity.

RESULTS

Basic characteristics of the patient population are presented in Table I. The incidence of arrhythmic events in the total population (7.6%), and in the subgroups of patients who did (6.2%) and did not (8.5%) receive thrombolytic therapy is listed in Table II. In the group with thrombolysis, all arrhythmic events occurred in patients who received streptokinase <6 hours after the onset of symptoms. There were no significant differences between the groups with and without thrombolysis regarding age (56 ± 10 vs 57 ± 9 years), left ventricular ejection fraction (49 ± 15 vs 50 ± 14%), infarct site (47 vs 52% with anterior AMI), treatment with β blockers (28 vs 32%), or history of AMI (7 vs 14%).

Comparison of signal-averaged electrocardiographic variables: The statistical comparison of individual signal-averaged electrocardiographic variables in pa-

tients with and without arrhythmic events is shown in Table III. Although the differences were highly significant in patients who did not receive thrombolytic therapy, only the RMS-40 values were significantly different (p value close to nonsignificance) in patients with thrombolysis.

Performance of diagnostic categoric criteria: The performance of the categoric criteria for signal-averaged electrocardiographic diagnosis (listed in the Methods section) is shown in Table IV. Both criteria performed better in the subgroup of patients who did not receive streptokinase; the positive predictive accuracy was >3 times higher in this group than in those with thrombolysis.

With both criteria, there was no significant difference between the incidence of abnormal signal-averaged electrocardiographic diagnosis between patients with and without thrombolysis (criterion 1: 19.2 vs 11.4%; and criterion 2: 18.5 vs 11.9%).

Retrospective risk stratification: With hindsight, dichotomy points can be chosen that optimize the sensitivity for any given specificity. The relation between the optimum positive predictive accuracy and sensitivity is shown in Figure 1.

Although it was possible to adjust the diagnostic criteria in order to achieve 100% positive predictive accuracy for up to 30% sensitivity in the subgroup of patients without thrombolysis, the maximum achievable positive predictive accuracy in the subgroup with thrombolysis was <30%.

DISCUSSION

Study findings: Several studies reported the relation between thrombolysis and patency of the infarct-related

TABLE III Values of Signal-Averaged Electrocardiographic Variables in All Patients, and in Those With and Without Thrombolysis				
Variable	Group	VT/SD	Others	p Value
tQRS	All	115 ± 18.4	102 ± 17.1	0.0002
	TT not used	116 ± 19.4	100 ± 16.4	0.0008
	TT used	114 ± 17.3	104 ± 18.0	0.0699
RMS-40	All	29.5 ± 23.8	67.7 ± 51.4	0.0000
	TT not used	29.5 ± 27.1	72.6 ± 54.0	0.0001
	TT used	29.4 ± 16.1	60.4 ± 46.4	0.0419
LAS	All	37.8 ± 17.3	25.3 ± 11.8	0.0001
	TT not used	40.2 ± 19.0	23.7 ± 10.3	0.0001
	TT used	32.8 ± 12.7	27.6 ± 13.4	0.1186

For each signal-averaged electrocardiographic variable, table shows mean value ± standard deviation found in patients with arrhythmic events (VT/SD) and in other patients (Others). These values are shown for total patient population (All), and for those who did and did not receive thrombolytic therapy (TT). Values of statistical significance (Mann-Whitney U test) of differences between patients with arrhythmic events and others are shown.
LAS = duration of low-amplitude signals <40 μv; RMS-40 = root-mean-square voltage of terminal 40 ms of signal-averaged QRS complex; SD = sudden death; tQRS = total duration of signal-averaged QRS complex; VT = ventricular tachycardia.

TABLE IV Performance of Categoric Criteria for the Diagnosis of Signal-Averaged Electrocardiography in All Patients, and in Those With and Without Thrombolysis									
Criterion	Population	TP	TN	FN	FP	Sen	Spc	PPA	p Value
(1)	All	12	270	13	36	48	88	25	4.9×10^{-6}
	TT not used	9	170	8	14	53	92	39	7.4×10^{-5}
	TT used	3	100	5	22	38	82	12	0.01
(2)	All	12	270	13	36	48	88	25	4.9×10^{-6}
	TT not used	9	169	8	15	53	92	38	0.0001
	TT used	3	101	5	21	38	83	12	0.008

For categoric criteria (1) and (2) (see text), numbers of true positive (TP), true negative (TN), false negative (FN) and false positive (FP) patients when using the criterion for the prediction of arrhythmic events in the complete patient population (All), and in groups of those who did and did not receive thrombolytic therapy (TT) are shown. Values of statistical significance of association of positive outcome of criterion with arrhythmic events (Fisher exact test) are shown.
PPA = positive predictive accuracy (%); Sen = sensitivity (%); Spc = specificity (%).

FIGURE 1. *Curves* show maximum retrospectively achievable positive predictive accuracy for different values of sensitivity for prediction of arrhythmic events (see Methods section in text). *Fine full line* corresponds to complete population, *bold full line* to subgroup of patients who did not receive thrombolytic therapy, and *dotted line* to group of patients with thrombolysis.
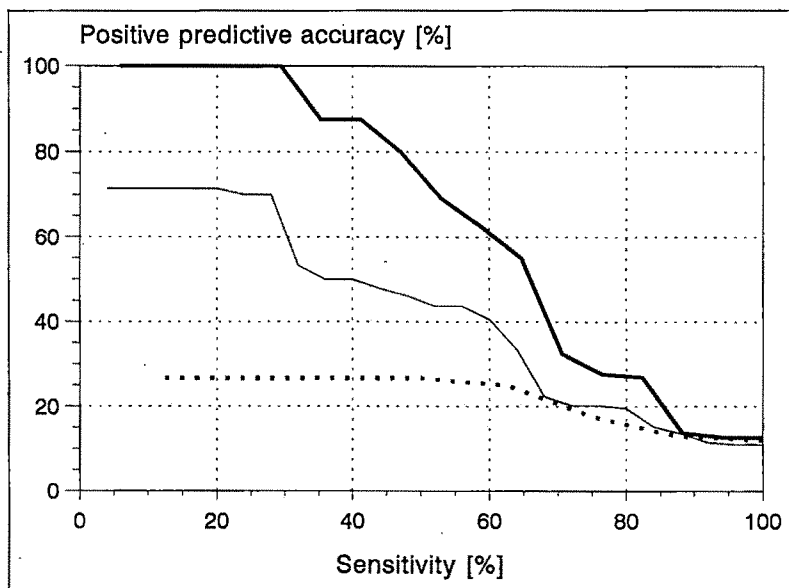
artery,[12,19] and showed the reduced incidence of late potentials in patients with thrombolysis.[10–12] It was suggested that reperfusion of the infarct-related artery has a beneficial effect on the electrophysiologic substrate for serious ventricular arrhythmias, because successful thrombolysis reduces the probability of the development of a large area of slow conduction with arrhythmogenic properties, which may manifest as a detectable late potential.

However, with both categoric criteria for signal-averaged electrocardiographic diagnosis, there was no significant difference between the incidence of abnormal findings in the groups with and without thrombolysis. This study examined a large post-AMI population compared with previous studies that reported a lower incidence of late potentials among patients with thrombolysis. The group with thrombolysis included all patients who received streptokinase, and we did not verify the success of thrombolysis by cardiac catheterization. Thus, the results are consistent with those reported by Turitto et al[9] who found significant signal-averaged electrocardiographic differences only between patients with and without successful thrombolysis, but not between groups with and without thrombolysis. Our protocol also included administration of streptokinase up to 24 hours after the onset of symptoms. Hence, the impact of thrombolysis in our study group may have been different compared with that in studies restricted to much earlier administration.[9,20] Although all patients with thrombolysis who had arrhythmic events received streptokinase within 6 hours after the onset of symptoms, the inclusion of those receiving thrombolytic therapy late may have influenced the predictive importance of signal-averaged electrocardiography.

The reduction of arrhythmic events in AMI survivors with successful thrombolysis[10] may be solely explained by the reduction in the development of arrhythmogenic regions with slow conduction. Some patients may have a different arrhythmogenic substrate that does not manifest on signal-averaged electrocardiography and that may be more or less affected by reperfusion. A hypothesis of a complex and indirect effect of thrombolytic intervention on the substrate for arrhythmic events may also be supported by the observation of newly developed late potentials after successful recanalization.[11]

The reduction of abnormalities on signal-averaged electrocardiography after successful reperfusion has also been observed without the reduction of complex acute ventricular arrhythmias.[20] This, together with the observation of new late potentials after recanalization,[11] suggests that the therapeutic mechanisms of thrombolysis are more complex than were originally believed. This agrees with our finding that both the sensitivity and specificity of categoric criteria for late potential diagnosis were reduced in patients with thrombolysis.

Although the relation between positive signal-averaged electrocardiographic findings and arrhythmic events after AMI has been clearly demonstrated,[1–7] not all mechanisms involved are clearly understood. It is even possible that by remodeling the infarcted area, thrombolytic therapy may be proarrhythmic in some cases and be antiarrhythmic in others, especially when not used immediately after the onset of symptoms (e.g., >4 hours, as was the case with a large portion of our population). A combination of such mechanisms with a complex influence of thrombolytic therapy on the incidence of late potentials may explain the findings of this study, and the difference from studies that administered thrombolytic agents much earlier.[12]

Our investigation was confined to the standard time domain signal-averaged electrocardiographic variables and the 25 to 250 Hz filter setting. Spectral analysis, especially when applied to the complete signal-averaged QRS complex,[21] may provide useful independent information. Other innovative techniques of signal-averaged electrocardiographic analysis[22] may also provide prognostically useful information in patients with thrombolysis.

Study limitations: The most important limitation of this study is the small number of arrhythmic events (especially in the group with thrombolysis). However, the differences between the predictive value of signal-averaged electrocardiography in the groups with and without were marked (Figure 1), and therefore, we believe that they are not caused by the lack of data.

The group without thrombolysis included both patients admitted before the second half of 1988 and those admitted later who were not eligible for treatment with streptokinase. Thus, the data of the groups with and without thrombolysis were not collected exactly contemporarily. This may have had a bearing on the incidence of late potentials.

We did not relate the findings of this study to other recognized risk stratification factors (e.g., left ventricular ejection fraction, ventricular ectopy or heart rate variability). Although the effect of thrombolytic therapy on novel stratification factors needs investigation, the reperfusion of an infarct-related artery has been reported not to have a significant effect on left ventricular ejection fraction.[19] This is in agreement with our observations and suggests that the predictive value of late potential diagnosis in the group with thrombolysis would not be substantially improved by its combination with left ventricular ejection fraction. However, multivariate analysis of a large cohort of patients with thrombolysis is needed to examine this properly.

All recordings were obtained when patients were not treated with antiarrhythmic drugs that are likely to influence signal-averaged electrocardiographic variables; we did not investigate differences in the predictive power of late potentials in patients with thrombolysis who were and were not treated with β blockers. However, other reports showed that these drugs do not significantly influence signal-averaged electrocardiographic analysis.[23] Because the incidence of treatment with β blockers was similar in the groups with and without thrombolysis, the effect of β blockers could not have influenced our major findings.

The 2 categoric criteria used for the diagnosis of signal-averaged electrocardiography were selected arbitrarily from many different criteria published by other investigators. Furthermore, criterion (1), which was proposed by the joint American College of Cardiology,

American Heart Association and European Society of Cardiology task force committee,[17] was suggested for signal-averaged electrocardiographic variables derived at filter settings of 40 to 250 Hz, whereas our study used settings of 25 to 250 Hz. However, the findings obtained with both criteria were consistent, and the retrospectively computed receiver-operator characteristics, as well as the curves presented in Figure 1, showed that any categoric criterion was likely to perform better in the subgroup of patients who did not receive streptokinase.

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Six-Year Survival After Coronary Thrombolysis and Early Revascularization for Acute Myocardial Infarction

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Six-year follow-up was conducted in a consecutive series of 192 patients receiving thrombolytic therapy for acute myocardial infarction (AMI) with ST-segment elevation. Cardiac catheterization was performed within a day, and patients with an open infarct artery routinely had early revascularization: 99 (67%) underwent coronary bypass surgery and 18 (12%) coronary angioplasty. With this treatment strategy, 6-year cardiac mortality was 14.5%, 6% (12 patients) in hospital and 9% (16 patients) for survivors of hospitalization. Multivariate analysis showed that predictors of cardiac death among survivors of hospitalization were a closed infarct artery at catheterization (p <0.01), diabetes (p <0.01) and anterior myocardial infarction (p = 0.01). A subset of 146 patients underwent radionuclide angiography before hospital discharge; for them, predictors of mortality were a closed infarct artery at catheterization (p <0.01), anterior wall AMI (p = 0.02), and Killip class III to IV on admission (p <0.06). Left ventricular ejection fraction was not a significant predictor of mortality for this subset of patients.

(Am J Cardiol 1992;70:26–30)

There have been few prospective follow-up studies of patients treated with thrombolytic therapy for acute myocardial infarction (AMI). Mathey et al[1] described a 4-year follow-up of 227 patients treated with streptokinase early during AMI, and reported improved survival with an open infarct artery. They also found that coronary artery bypass grafting had an added survival benefit. In this report we present 6-year follow-up of patients having thrombolytic therapy for acute, transmural myocardial infarction and specifically examine clinical and angiographic variables that predict late mortality. We have found that a closed infarct artery soon after thrombolytic therapy, diabetes and anterior location of AMI were predictors of late cardiac death independent of left ventricular function.

METHODS

This study includes 192 consecutive patients with transmural AMI treated with intracoronary or intravenous streptokinase who were followed for >5 years. Selection criteria for thrombolytic therapy, contraindications, treatment protocols and early clinical course have been reported.[2,3] Patients aged ≤70 years, with chest pain lasting <6 hours unresponsive to sublingual nitroglycerin, and with ≥0.2 mV ST-segment elevation, were treated.

Intracoronary streptokinase was used during the first 11 months of the study. Patients were brought to the cardiac catheterization laboratory as quickly as possible after diagnosis of transmural myocardial infarction and treated with an initial intracoronary streptokinase bolus of 30,000 U followed by 3,000 U of intracoronary streptokinase per minute for 60 minutes. Heparin was started immediately after intracoronary streptokinase in patients with arterial opening.

During the subsequent 13 months of the study patients were treated with intravenous streptokinase. This was given in the emergency room as soon as the diagnosis of myocardial infarction was confirmed by the primary care physician. A "front loaded" dosing regimen was used, with an initial dose of 500,000 U over 5 minutes followed by 200,000 U/hour for 4 hours. Heparin was then started at 1,000 U/hour, and the dose was adjusted to maintain activated partial thromboplastin time 70 to 100 seconds. Patients treated with intravenous streptokinase in community hospitals were transferred for angiography as soon after the initial streptokinase bolus infusion as possible, and most had angiography within 24 hours.[2,3] Heparin was discontinued

with documented absence of thrombolysis (patients with intravenous streptokinase) or at the time of revascularization (both intracoronary and intravenous streptokinase).

Early revascularization was routinely recommended for patients with an open infarct artery and critical stenosis of the infarct artery (reduction of luminal diameter by ≥70%). Revascularization was performed during the same hospitalization as soon as it could be scheduled and after clotting function had returned to normal. Percutaneous transluminal coronary angioplasty or coronary artery bypass surgery was performed using standard techniques, and details of our early experience have been reported.[2,3] Radionuclide angiography was performed in 146 of the 180 survivors of myocardial infarction before hospital discharge (142 patients), or within 2 months (4 patients). No attempt was made to standardize medical therapy after discharge, although all patients were treated with daily aspirin.

Follow-up was conducted between December 1988 and April 1989. This series included all patients treated with thrombolytic therapy before September 1983. Follow-up was achieved for all 180 survivors of hospitalization in the series by a nurse researcher by telephone or clinic visit. The primary end point was cardiac death defined as sudden death, death after AMI, or death after hospitalization for congestive heart failure. The effect of each clinical and angiographic variable on cardiac mortality for patients surviving hospitalization was analyzed by chi-square and t test for unpaired variables. Cox's proportional hazards regression was subsequently used to analyze the relation (if any) among clinical and angiographic variables affecting survival.[4] The Cox model was also used to calculate an estimated survival function adjusted for the combination of variables found to be significant. An additional regression analysis was performed for a subset of patients having predischarge radionuclide angiograms. All values are expressed as mean ± 1 standard deviation.

RESULTS

During 24 months, 192 patients with transmural myocardial infarction were treated with intracoronary (n = 75) or intravenous (n = 117) streptokinase. Twelve patients (6%) died before hospital discharge (2,3). Follow-up data were obtained for all 180 survivors of hospitalization a minimum of 5 years after myocardial infarction. During follow-up, 21 of the 180 patients died (11.7%). Average follow-up for the 159 survivors was 74 ± 7 months. There were 16 cardiac deaths (9%) (Figure 1); 7 had recurrent AMI, 6 had congestive heart failure, 2 died suddenly, and 1 died after coronary bypass surgery. Subsequent mortality analysis will consider only these 16 patients with cardiac death.

Clinical characteristics: The hospital course of the initial cohort of 192 patients has been described.[2,3] The average patient in this follow-up study of 180 survivors was aged 55 ± 10 years, and clinical characteristics are outlined in Table I. All patients had ST-segment elevation and chest pain at the time of streptokinase therapy and, as reported, all subsequently had elevation of creatine kinase.[2] Streptokinase therapy was begun 202 ± 92 minutes after onset of chest pain. An open infarct artery was identified at cardiac catheterization in 137 of the 180 survivors of hospitalization (76%). Early angiography was attempted in the 111 patients treated with intravenous streptokinase; the interval from initiation of therapy to catheterization was 1 to 4 hours for 46 (41%), 4 to 12 hours for 20 (18%), 12 to 24 hours for 19 (17%), 24 to 48 hours for 17 (15%), and 2 to 4 days for 9 (8%).

Early revascularization while in the hospital after AMI was performed an average of 3 ± 2 days after streptokinase treatment in 111 of the 137 patients (81%) with an open infarct artery at catheterization; 94 (69%) had coronary artery bypass surgery and 17 (13%) had successful percutaneous transluminal coronary angioplasty. Bypass patients received 3 ± 1.4 grafts per patient. Angioplasty was attempted in 22 pa-

FIGURE 1. Cumulative probability of cardiac survival for 180 patients who survived hospitalization and were followed 74 ± 7 months after myocardial infarction with ST-segment elevation.
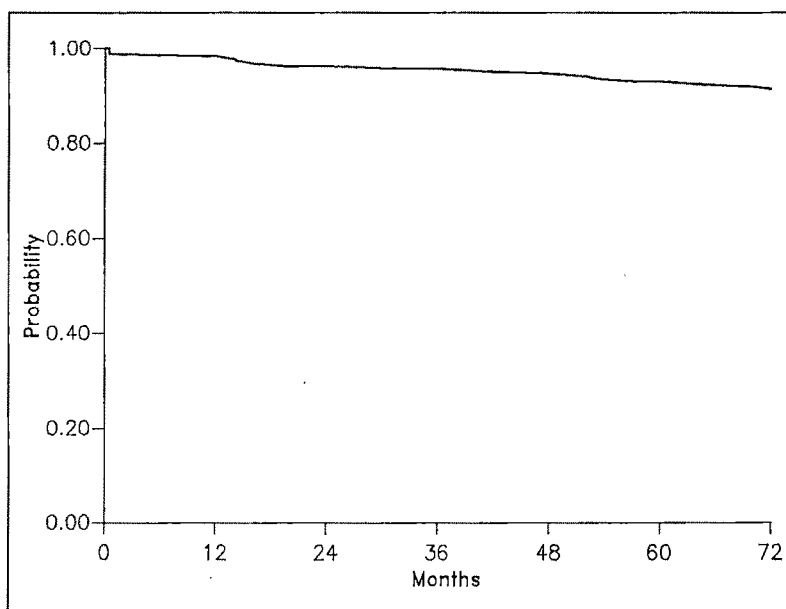
TABLE I Clinical Variables and Six-Year Follow-Up of 180 Survivors of Hospitalization

	No. of Pts.	Cardiac Death (%)	p Value
All patients	180	16 (9%)	
Age ≥65 years	32	3 (9%)	NS*
Women/men	33/147	5 (15%)/11 (7%)	NS
Cigarette use†	119	11 (9%)	NS*
Systemic hypertension	63	7 (11%)	NS*
Diabetes mellitus	27	7 (26%)	<0.001*
Prior AMI	32	5 (16%)	NS*
Anterior AMI	66	10 (15%)	
Inferior AMI	114	6 (5%)	0.025
Onset of AMI to Rx‡			
≤3 hours	79	5 (6%)	NS
>3 hours	99	11 (11%)	NS
Killip I–II§	168	13 (8%)	
Killip III–IV	12	3 (25%)	0.042
Open infarct artery	137	8 (6%)	
Closed infarct artery	43	8 (19%)	0.024
0–1-vessel disease‖	107	6 (6%)	
2-vessel disease	48	6 (13%)	NS
3-vessel disease	25	4 (16%)	
Follow-up RNA¶			
LVEF <40%	30	6 (20%)	
LVEF ≥40%	116	7 (6%)	0.039
Revascularization**			
CABS	102	7 (7%)	
PTCA	20	2 (10%)	NS
Neither	58	7 (12%)	

*Compared with those not having this characteristic.
† ≥20-pack/year history at time of AMI.
‡ Data not available for 2 patients.
§Killip class at time of admission.
‖Stenosis defined as ≥70% reduction of luminal diameter. Cardiac mortality with multivessel (10 of 73) versus nonmultivessel (6 of 107); coronary artery disease p = 0.06.
¶RNA not recorded in 34 patients.
**Including patients with open and closed infarct arteries.
AMI = acute myocardial infarction; CABS = coronary artery bypass surgery; LVEF = left ventricular ejection fraction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; RNA = radionuclide angiogram; Rx = thrombolytic therapy.

tients and was initially successful in 21 (95%); 4 had reocclusion within 1 hour of angioplasty. Angioplasty thus was ultimately successful in 17 (77%), and the 5 with unsuccessful angioplasty underwent urgent coronary bypass surgery.

Early revascularization was not performed in 26 of the 137 patients with an open infarct artery; 1 refused coronary artery bypass surgery, 3 had documented reocclusion of the infarct artery within 24 hours of streptokinase therapy, 7 had either minimal stenosis or normal-appearing infarct arteries, 3 had infarction due to occlusion of a small artery and single vessel disease, 2 had bypass surgery delayed 60 days because of intracranial bleeding and sepsis, respectively, and 10 had 1-vessel coronary disease and were believed to have had little salvage of myocardium as a result of treatment late in the course of the infarction or akinesia of the infarct zone both at initial and late ventriculographic study.

Eleven of 43 patients in the group in which streptokinase was unsuccessful (closed infarct artery at catheterization) underwent early revascularization; 8 underwent coronary artery bypass surgery because of multivessel disease, 2 had successful angioplasty of an occluded artery during the acute phase of infarction (and are included in the unsuccessful streptokinase

group for purposes of analysis), and 1 had angioplasty of a noninfarct artery.

Univariate predictors of survival: Clinical features and follow-up cardiac mortality are summarized in Table I. Significant univariate predictors of survival included location of myocardial infarction, follow-up ejection fraction, diabetes, Killip class on admission and an open infarct artery. Location of infarction and subsequent left ventricular function were closely related; patients with anterior infarction had a predischarge ejection fraction of 41 ± 15, and those with inferior infarction had a predischarge ejection fraction of 58 ± 11 (p <0.001). Similarly, Killip class at the time of hospital admission correlated with late ejection fraction; patients with Killip class I to II had a late ejection fraction of 52 ± 15, and those with Killip class III to IV had a late ejection fraction of 44 ± 17 (p = 0.08).

Multivariate analysis: Cox's proportional hazard regression model was used to study the relation among clinical and angiographic variables (Table I). Significant predictors of late cardiac death (excluding late ejection fraction as a variable) were diabetes (p <0.01), a closed infarct artery at cardiac catheterization (p <0.01) and anterior wall AMI (p = 0.01). Thus, for patients with and without diabetes mellitus, those with anterior myocardial infarction had higher late mortality (Figure 2). Furthermore, within the high risk group with anterior infarction, those with an open infarct artery had a better prognosis. Lower risk patients with inferior infarction also fared better with an open infarct artery (Figure 2). Among the highest risk, diabetic patients, those with anterior wall AMI and closed artery had 75% cardiac mortality in 6 years compared with a 33% mortality rate for similar diabetic patients and anterior infarction who had an open infarct artery.

Cox's hazard function analysis was repeated for the subgroup of 146 patients who underwent radionuclide angiography during the late hospital phase. In this analysis low ejection fraction was not a significant predictor of cardiac death. Instead, a closed infarct artery at catheterization (p <0.01), anterior infarction (p = 0.02) and Killip class III to IV (p <0.06) predicted mortality.

DISCUSSION

The purpose of this observational trial was to provide prognostic information, and it is the longest available follow-up study of patients treated with thrombolytic therapy for AMI. The 6-year cardiac mortality for 192 patients initially treated with streptokinase was 14.5%. The cardiac mortality for the 180 survivors of hospitalization was 9%. Multivariate analysis identified a closed infarct artery, diabetes mellitus and anterior location of the AMI as risk factors for late cardiac death among survivors of hospitalization.

Mathey et al[1] reported 4-year follow-up survival data for a similar series of 227 patients treated with thrombolytic agents; 4 year mortality was 18%. They found an association of an open infarct artery and improved survival and further reported that patients with an open infarct artery who had coronary artery bypass grafting had improved survival. We did not identify by-

FIGURE 2. Effect of diabetes mellitus, an open infarct artery at cardiac catheterization and infarct location on cumulative probability of cardiac survival over 6 years. Multivariate Cox's hazard function analysis showed that these were significant, independent predictors of cardiac mortality. A, nondiabetic patients; B, diabetic patients.
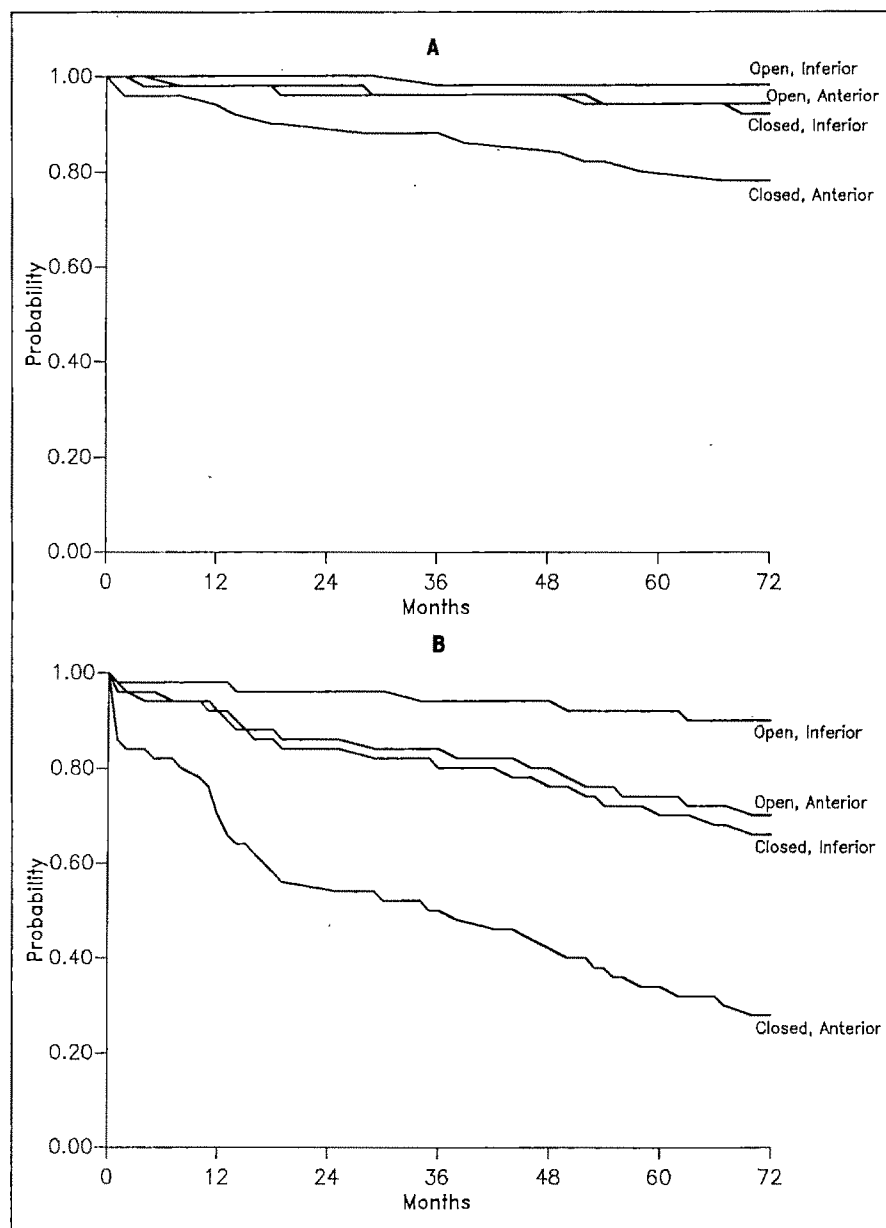
pass grafting as an independent predictor of late survival, possibly because more of our patients had revascularization (68 vs 48%) and bypass grafting (57 vs 22%) when compared with Mathey's study. A higher percentage, if not most patients who might have benefited from bypass grafting, underwent it in our trial.

Both of these studies identified an open infarct artery as a predictor of survival independent of changes in left ventricular function. Whereas the results support the "open artery hypothesis," they do not prove it, as neither was a controlled study.[5-9] Furthermore, the high association of an open infarct artery and revascularization in these studies makes it hard to determine which of the 2, reperfusion or revascularization, is most important in determining long-term outcome. Mathey claimed that bypass surgery helped. Our results do not support that claim. On the other hand, the Thrombolysis in Myocardial Infarction trial, a controlled study of

"revascularization" after reperfusion therapy, failed to show any short-term survival benefit.[10] But this study routinely used early angioplasty of the culprit lesion, not coronary bypass surgery, the approach most often taken in our study and the Mathey trial.

Our data provide an estimation of late prognosis after AMI using a treatment strategy of thrombolysis and early revascularization. There are no late survival data for patients having medical treatment or angioplasty as routine therapy after coronary thrombolysis. The present results should not be used to advise such patients about prognosis, since late mortality must be influenced both by thrombolysis and subsequent therapy.

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Value of Negative Predischarge Exercise Testing in Identifying Patients at Low Risk After Acute Myocardial Infarction Treated by Systemic Thrombolysis

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Although thrombolytic therapy reduces mortality in patients with acute myocardial infarction (AMI), it is associated with a greater incidence of successive coronary events, and there is still no ideal diagnostic and therapeutic strategy for such patients. The present study verifies the value of negative predischarge exercise testing in identifying low-risk patients treated with thrombolysis after AMI. One hundred fifty-seven consecutive patients with an uncomplicated clinical course underwent maximal or symptom-limited exercise testing (Bruce treadmill protocol) within 15 days of AMI in the absence of therapy. The location of the AMI was anterior in 51 patients, inferior in 85 and non-Q-wave in 21. All of the patients were followed for 6 months. Death and nonfatal reinfarction were considered as major coronary events, and the recurrence of angina as a minor event. Exercise test results were negative in 105 patients (group 1) and positive for angina or ST depression $\geq$0.1 mV in 52 (group 2). No deaths occurred during follow-up; there were 3 reinfarctions (3%) and 7 cases (7%) of postinfarction angina in group 1, and 2 reinfarctions (4%) and 21 cases (40%) of postinfarction angina in group 2. By the end of follow-up, 90% of the patients with negative exercise test results were event-free (97% in the case of major events). These results show that thrombolytic therapy does not affect the value of negative postinfarction exercise testing in identifying low-risk patients.

(Am J Cardiol 1992;70:31–33)

Fibrinolytic therapy has radically changed the natural history of patients with acute myocardial infarction (AMI). Studies involving large numbers of patients have shown that such treatment leads to a significant reduction in hospital mortality and that this advantage continues over the long term.[1-4] Nevertheless, a high percentage of patients also have important coronary stenoses at the site of the infarct and this may limit myocardial recovery in the acute phase and cause early or late reocclusion.[5,6] Before the introduction of thrombolytic therapy, exercise testing was the most widely used method of evaluating uncomplicated AMI, given that <2% of patients with a negative maximal exercise test result died within 1 year and that there was usually no need for further diagnostic evaluation.[7-10] However, it is possible that what is true for patients treated with conventional therapy may not be true for patients treated with thrombolytic therapy.[11,12] The present study verifies whether a negative exercise test response is still capable of identifying patients at low risk after uncomplicated AMI in the era of thrombolytic therapy.

METHODS

Study population: The characteristics of the study population are shown in Figure 1. Between January 1988 and October 1990, 708 patients were admitted to our intensive coronary care unit for AMI. The presence of $\geq$2 of the following criteria led to a diagnosis of AMI: typical chest pain lasting for >30 minutes; Q waves that were abnormal according to the Minnesota Code,[13] with evolutionary ST and T waves changes on serial tracings; an increase in total serum creatine kinase, with a peak level of more than twice the upper limit of the normal values for our laboratory; and the presence of an MB isoenzyme fraction >5% of total creatine kinase. Of the 708 admitted patients, 292 received intravenous systemic thrombolytic treatment (streptokinase 1,500,000 U over 60 minutes or recombinant tissue-type plasminogen activator 100 mg over 3 hours). Thrombolytic treatment was administered to all of patients admitted within 6 hours of the onset of symptoms and who had typical chest pain persisting for >30 minutes and ST-segment elevation $\geq$1 mm in $\geq$2 adjacent electrocardiographic leads. During the acute phase, 17 of these patients died (mortality 5.8%); the remaining 275 were considered eligible for the present prospective study. Of these 275 patients, 157 underwent exercise

FIGURE 1. Study population. AMI = acute myocardial infarction; CCU = coronary care unit; ET = exercise test; ITT = intravenous thrombolytic therapy.

and then every 3 minutes until the electrocardiogram returned to normal. During exercise, 3 leads were continuously monitored. End-point criteria were: (1) angina, (2) ST depression >0.2 mV, (3) dyspnea, (4) complex ventricular arrhythmias, (5) a decrease in systolic blood pressure >10 mm Hg in 2 consecutive steps, and (6) fatigue. The presence of angina or ST-segment depression ≥0.1 mV, measured at 80 ms from the J point, were considered as criteria of positivity.

Follow-up: Patients were controlled by means of clinical visits 6 months after AMI. All were treated with β blockers and aspirin if these were well tolerated. Death and nonfatal reinfarction were classified as major events, and postinfarction angina as a minor event. Angioplasty and coronary artery bypass grafting, although not considered events as such, were also taken into account. Follow-up was concluded in all patients.

Statistical analysis: Values are presented as mean ± standard deviation. The chi-square test was used to compare the incidence of discrete variables between groups. A p value <0.05 was considered significant.

RESULTS

Of the 157 enrolled patients, 136 were men (86%) and 21 women (14%) (mean age 55 ± 11 years [range 34 to 76]); the location of the AMI was anterior in 51 patients (32%), inferior in 85 (54%) and non-Q-wave in 21 (14%).

Exercise test results were negative in 105 patients (group 1) and positive for angina or ST depression in 52 (group 2). Mean duration of exercise was 7 ± 2 minutes, peak heart rate 135 ± 15 beats/min, and peak systolic blood pressure 170 ± 29 mm Hg. No deaths occurred during the 6-month follow-up period; 5 patients (4%) experienced a reinfarction, angina appeared in 28 (18%) and 19 (12%) underwent revascularization. In group 1, there were 3 reinfarctions (3%) and 7 cases of angina (7%); in group 2, there were 2 reinfarctions (4%) and 21 cases of angina (40%) (Figure 2). There were no differences between the 2 groups with regard to reinfarction, but there was a significant difference in the appearance of angina (p <0.001). Three of the patients in group 1 underwent revascularization (3%) by means of angioplasty and 16 patients in group 2 (30%) had revascularization by means of bypass grafting (n = 12) and angioplasty (n = 4) (p <0.001). By the end of follow-up, 90% of the patients with negative exercise test results were event-free (97% had no major events).

testing and 118 were excluded from the study for the following reasons: postinfarction angina in 36, clinical signs of left ventricular dysfunction in 19, complex ventricular arrhythmias in 2, constant pacemaker rhythm in 2, stable left bundle branch block in 7 and physical limitations precluding maximal testing in 52. Advanced age was not considered an exclusion criterion; none of the patients underwent angiography before the test.

Exercise testing: All of the patients performed a maximal or symptom-limited treadmill exercise test according to the Bruce protocol, in the absence of antianginal therapy, within 15 days of AMI (mean 12 ± 2 days). Blood pressure and 12-lead electrocardiographic recordings were obtained at rest, at the first and third minute of every stage of exercise, at the end of exercise, at the first and the third minute of the recovery period,

FIGURE 2. Follow-up results at 6 months. ET = exercise test; ns = not significant.

DISCUSSION.

Although systemic thrombolytic therapy has been shown to be capable of limiting the extension of AMI and reducing both hospital and long-term mortality, it is also associated with an increased risk of successive coronary events.[1-4] The ideal diagnostic approach to adopt for patients treated with thrombolytic therapy is not yet known. In particular, it is not known whether a negative exercise test result is sufficiently indicative of patients at low risk for cardiac events, as is the case with conventionally treated patients.[12] Our study shows that the enrolled population, consisting of a consecutive series of patients treated with thrombolytic therapy with an uncomplicated clinical course, had good prognosis as far as major events were concerned. This is attributable not only to thrombolysis but also to the combination of 2 selection factors: (1) Among patients surviving an infarct, those eligible for an early predischarge exercise test (62% in our series) have a particularly good prognosis[9,14,15]; and (2) accepted exclusion criteria ensure that patients eligible for thrombolysis have a lower rate of mortality than the global population of patients with AMI.[16]

The exercise test results from our study show that patients with a negative exercise test response have an excellent prognosis with an overall negative prediction of cardiac events of 90% (97% in major events). Only 3 patients (3%) underwent revascularization within 6 months, and so it is unlikely that recourse to revascularization significantly modified the prognosis in these patients. Our results are similar to those relating to published studies on a large number of patients during the prethrombolytic era. These studies have demonstrated that patients with a negative exercise test result have a 1-year mortality rate <2%, and that the negative predictive value for cardiac events (death and reinfarction) is 95%.[9,15,17]

During follow-up of patients with positive exercise test results, one should remember that it was beyond the scope of the present study to verify the predictive value of postinfarct positivity. Historical studies have clearly shown that positive results identify a group of patients with a high mortality rate[8] and that this can be favorably modified by revascularization,[18] which may distort the relation between parameters such as ST-segment depression and cardiac mortality. As expected, in our study population, a positive exercise test response correlated with the appearance of postinfarction angina and revascularization, but there was no correlation with major clinical events (death or reinfarction). This agrees with the results of more recent studies demonstrating that a positive postinfarction exercise test is not predictive of mortality or reinfarction: mortality is correlated with indexes of ventricular dysfunction, such as exercise duration and the behavior of blood pressure, and no ergometric index is predictive of reinfarction.[14,15,17,19,20]

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Magnetic Resonance Imaging During Dobutamine Stress in Coronary Artery Disease

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Cine magnetic resonance imaging (MRI) provides a tomographic method of assessing regional ventricular function in any desired plane. It has not been possible to obtain adequate images during dynamic exercise, and this has limited its value in patients with coronary artery disease (CAD). Therefore, an infusion of dobutamine was used to study 25 patients with exertional chest pain and abnormal exercise electrocardiograms. Areas of abnormal wall motion were compared with areas of abnormal myocardial perfusion imaged by dobutamine thallium emission tomography and with coronary arteriography. Twenty-two patients had significant CAD. Twenty-one (96%) of these patients had reversible myocardial ischemia shown by dobutamine thallium tomography, and 20 (91%) had reversible wall motion abnormalities shown by dobutamine MRI. Comparison of abnormal segments of perfusion and wall motion showed 96% agreement at rest, 90% agreement during stress, and 91% agreement for the assessment of functional reversibility. The normalized magnetic resonance signal intensity of the ischemic segments showed a small but significant reduction when compared with that of normal segments (−67 units [9.2%]; p <0.05). Dobutamine infusion was well-tolerated, despite causing chest discomfort in 24 patients (96%). Nine patients (36%) developed a minor dysrhythmia that was usually ventricular premature complexes, but this did not limit infusion, and other side effects were mild. The short plasma half-life of dobutamine makes it ideal as a stress agent for imaging techniques (such as MRI), and these results suggest that it is more effective in the provocation of wall motion abnormalities than is dipyridamole in patients with CAD.

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Magnetic resonance imaging (MRI) is an excellent method of assessing structure and function of the cardiovascular system. It provides high-resolution tomographic images with excellent soft tissue contrast, cine images for the study of ventricular and valvular function, and velocity and flow measurements within the heart and vessels. Because of the need to use electrocardiographic triggering over many cardiac cycles it is difficult to image during dynamic exercise. The problem may be partly overcome by rapid imaging techniques such as echo planar[1] or rapid gradient echo[2] imaging, but these are not yet widely available. Therefore, there have been few studies of regional or global ventricular function during stress in patients with coronary artery disease (CAD).

We previously used cine MRI to study patients with CAD after infusion of dipyridamole,[3,4] but wall motion abnormalities were induced by dipyridamole in only 67% of those in whom defects of thallium uptake were seen.[4] This low sensitivity, the problem of maintaining coronary flow levels during imaging, and the difficulty in controlling side effects restrict the value of dipyridamole for MRI studies. Dobutamine may be used as an alternative form of pharmacologic stress, and was previously used during electrocardiography,[5] echocardiography,[6,7] thallium myocardial perfusion imaging[8,9] and radionuclide ventriculography.[10] We report the first use of dobutamine for the assessment of regional left ventricular function by MRI in patients with CAD.

METHODS

Patients: We studied 25 patients (22 men and 3 women, mean age 52 years, range 38 to 63) with history of exertional chest pain and an abnormal exercise electrocardiogram who were undergoing coronary arteriography. Eight patients had previous Q-wave myocardial infarction (7 inferior and 1 apical), and 3 had had non-Q-wave infarction (1 inferior and 2 anterior). No patient had clinical signs or symptoms of cardiac failure, or was receiving diuretic treatment. All patients were investigated by thallium tomography using dobutamine stress, cine MRI using dobutamine stress, and coronary arteriography. All studies were performed within a 2-week period without intervening clinical events. Six patients had disease of all 3 major coronary arteries, 10 had disease of 2 vessels, 6 had disease of 1 vessel, and 3 had no significant arterial stenosis. Patients with contraindications to MRI (pacemaker) or dobutamine stress were not studied, including those with valvular heart disease, hypertrophic cardiomyopathy, second- or third-degree atrioventricular conduction block, heart failure of New York Heart Association grade 2 or more, histo-

ry of ventricular dysrhythmia or adverse reaction to dynamic exercise, diastolic blood pressure >100 mm Hg or systolic blood pressure >200 mm Hg, or angina at rest within the previous month. Beta-blocking medication was discontinued 48 hours before dobutamine stress without adverse reaction, but all other medication was continued. The study was approved by the hospitals' ethical committees, and informed patient consent was obtained. The estimated radiation exposure to the patient from 80 MBq of thallium is 25 mSv.[11]

Stress: Dobutamine was infused in a peripheral vein with the patient in the supine position, using an IVAC 711 syringe pump (IVAC Corporation, San Diego, California). A 2 mg/ml solution was prepared using normal saline, and the initial infusion rate was 5 μg/kg/min. The infusion rate was increased every 5 minutes by steps of 5 μg/kg/min to a maximum of 20 μg/kg/min,[10] unless significant clinical events occurred, in which case imaging was performed at a dose just below the threshold for the clinical event. A significant event was deemed to be sustained dysrhythmia, diastolic blood pressure >110 mm Hg or systolic blood pressure >220 mm Hg, dyspnea, chest pain or other noncardiac side effect sufficient to cause patient discomfort. The electrocardiogram was monitored continuously (lead CM5), and blood pressure was recorded each minute during infusion, using an automatic pneumatic cuff system (Dinamap 845, Applied Medical Research, Tampa, Florida).

Thallium tomography: Eighty megabequerels of thallium were administered intravenously into a second cannula after hemodynamic equilibration at the peak infusion rate of dobutamine, which was then continued for a further minute. The immediate tomographic images were obtained after approximately 5 minutes, and redistribution images were obtained after 3 hours. A General Electric 400AZS gamma camera and a Star computer were used to obtain 32 planar images (64 X 64 pixel matrix, 400 mm field of view, 30 seconds/image) over a 180° arc from the right anterior oblique to the left posterior oblique projection. Transaxial tomograms of 1 voxel depth were reconstructed by back projection, using a Ramp-Hanning filter with a cutoff frequency of 0.75 pixel^{-1}. The transaxial tomograms were reoriented into oblique slices in the vertical and horizontal long- and short-axis planes.

Magnetic resonance imaging: Dobutamine was infused using small bore extension tubing with the patient in the magnet. The syringe pump was tested in the proximity of the magnetic field and found to function normally. The tubing was primed with the dobutamine solution, but the cannula was not primed, being left containing a solution of low-dose heparinized saline to prevent coagulation. After baseline imaging and without removing the patient from the scanner, the cannula was slowly flushed with 1 ml of dobutamine solution, and the infusion was then set to 5 μg/kg/min to begin the stress. At peak dose, wall motion images were repeated. At a typical stress heart rate of 120 beats/min, the imaging time for each cine was approximately 2 minutes.

A Picker International MR2055 scanner was used, operating at 0.5 Tesla. Cine imaging was performed using a sequence with gradient-refocused, velocity-compensated echoes in the vertical and horizontal long-axis, and apical and basal short-axis planes. To minimize magnetic saturation of blood at the apex in the long-axis planes, only 12 frames were obtained spanning all but the final 60 ms of diastole. Field of view was 40 cm, slice thickness 10 mm and echo time 14 ms, and 2 acquisitions of 128 phase-encoding steps were averaged. Images were interpolated from 128 X 256 to 512 X 512 pixels for display.

Coronary arteriography: Judkin's technique was used with multiple views of each vessel, and contrast left ventriculography was performed in the right anterior oblique projection.

Image analysis: All images were assessed by 2 experienced observers without knowledge of the results of other investigations, and disagreement was resolved by discussion. The left ventricular myocardium was divided in 9 segments by splitting the anterior, inferior and lateral walls, and septum into a basal and apical segment, and including an extra segment for the apex (Figure 1). Each segment was seen in 2 different planes. Segmental wall motion was characterized from cine magnetic resonance tomograms as normal, hypokinetic or akinetic, and segmental myocardial perfusion was characterized from thallium tomograms as normal, reduced or absent. If the appearance of a segment differed in the 2 planes in which it was seen, the worse of the 2 classifications was used. A dobutamine-induced wall motion abnormality was defined as a deterioration of ≥1 category. Dobutamine-induced myocardial ischemia was defined as impaired stress perfusion with redistribution of ≥1 category in the delayed images. Coronary arteriograms were assessed subjectively, and significant stenosis was defined as a reduction of ≥50% of the normal luminal diameter. Ventricular volumes were calculated by the
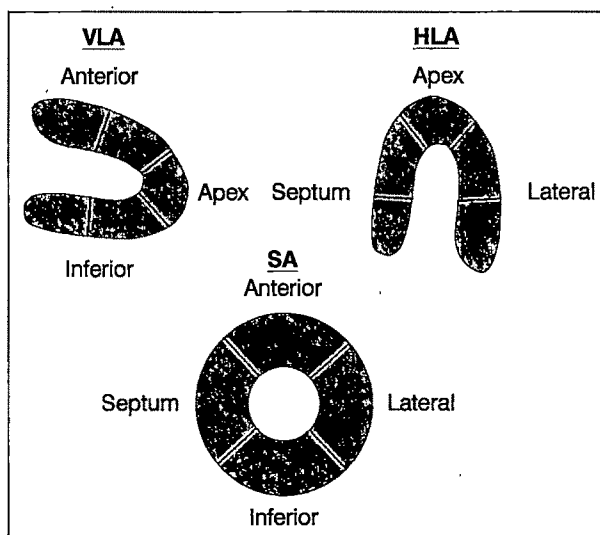
FIGURE 1. Planes used for analysis. Vertical long-axis plane (VLA) is obtained from transaxial plane by allowing for leftward angulation of left ventricle. Horizontal long-axis plane (HLA) is obtained from this by allowing for downward angulation of left ventricle. Short-axis plane (SA) is perpendicular to both. Each ventricular wall was divided in 2 segments, which with 1 apical segment made 9 segments for analysis in each patient.

TABLE I Mean Hemodynamic Changes of 25 Patients at Each Stage of the Dobutamine Infusion

Dose of dobutamine (μg/kg/min)	0	5	10	15	20
Systolic BP (mm Hg)	135	153	157	158	166
Diastolic BP (mm Hg)	77.3	76.5	75.9	76.2	77.7
Heart rate (beats/min)	71.4	84.4	97.3	113	119
Double product (×10³ mm Hg/min)	9.7	12.9	15.2	17.7	19.8

BP = blood pressure.

TABLE II Changes in Left Ventricular Volumes and Ejection Fraction from Baseline to Peak Stress in 25 Patients

	End-Diastolic Volume (ml)	End-Systolic Volume (ml)	Stroke Volume (ml)	Ejection Fraction (%)
Baseline	138	47.6	90.3	65.5
Peak stress	105	42.0	63.4	59.4
Change	−33	−5.6	−26.9	−6.1
p value	<0.001	<0.001	<0.001	<0.001

biplane area-length method, using the end-diastolic and end-systolic frames from the vertical and horizontal long-axis cines.[12]

The myocardial signal from the ischemic and normal myocardial regions was obtained by drawing a region of interest around the myocardium showing a new wall motion abnormality during stress, and using the same region of interest to determine the signal intensity in the corresponding baseline image. Regions of interest were drawn on the frame nearest to end-systole. The same technique was used to define the signal in normal myocardium and subcutaneous fat. The ratio of fat signal at baseline and during stress was multiplied by the stress myocardial signal for normalization to correct for changes in signal due to changes in the acquisition parameters used for imaging.

Statistical analysis: Hemodynamic changes during dobutamine infusion were analyzed using 2-way analysis of variance with repeated measures. Myocardial signal changes before and after dobutamine were analyzed using a paired t test. Distribution of the number of ischemic thallium segments and reversible wall motion segments according to the number of diseased coronary arteries was analyzed using the Spearman rank correlation coefficient. McNemar's test for comparison of 2 proportions was used to analyze the difference between thallium tomography and MRI in the detection of CAD. Changes in ventricular volumes and ejection fractions from baseline to peak stress were analyzed using a paired t test, and linear regression analysis was used to compare the volume and ejection fraction changes with the extent of myocardial ischemia as defined by thallium tomography. A p value ≤ 0.05 was considered significant.

RESULTS

Clinical effects of dobutamine: Dobutamine infusion produced chest pain or discomfort in 24 patients (96%), and was limited to 10 μg/kg/min in 5 and to 15 μg/kg/min in 9. The remaining 11 patients tolerated the full dose of 20 μg/kg/min. Other symptoms occurred in 19 patients (76%), including skin tingling (usually of the scalp) (n = 13), heart pounding (n = 5), mild nausea (n = 3), warmth (n = 3), dyspnea (n = 2), shaking (n = 1) and headache (n = 1). None of these symptoms needed termination of the stress, and most occurred at peak stress, except for skin tingling, which occurred as soon as the infusion began. Dysrhythmias were seen in 9 patients (36%) (7 ventricular premature complexes, 2 atrial premature complexes, 1 left bundle branch block, 1 sinus pauses and 1 nodal rhythm). No dysrhythmia was considered to be an indication for premature termination of stress.

Hemodynamic effects of dobutamine: The response in the 25 patients of blood pressure and heart rate to dobutamine infusion is shown in Table I. Systolic blood pressure, heart rate and double product increased significantly (p <0.001), but there was no change in diastolic blood pressure. At 20 μg/kg/min, systolic blood pressure increased by a mean of 31 mm Hg, heart rate by 48 beats/min, and double product by 10.1 × 10³ mm Hg/min. There was a significant decrease from baseline to peak stress in end-diastolic, end-systolic and stroke volumes, and ejection fraction (Table II). There was no significant correlation between the extent of change in these volume parameters and the extent of myocardial ischemia as determined by the number of segments of reversible myocardial perfusion abnormality.

Thallium tomography: Twenty-one of the 22 patients with CAD had abnormal thallium tomograms. The remaining patient had an occluded but nondominant circumflex artery with 60% narrowing of a diagonal branch of the left anterior descending artery. There was a significant correlation between the number of segments with perfusion defects and the extent of the CAD: patients with 3-, 2-, 1- and no vessel disease had an average of 5.2 (range 4 to 7), 4.7 (0 to 7), 2 (1 to 4) and 3 (2 to 4) abnormal segments, respectively (r_s = 0.58; p <0.005). There was a wide range of defect size in each group, and the 3 patients with no significant arterial stenosis were also found to have abnormal perfusion. All 8 patients with previous Q-wave infarction had defects in the redistribution tomograms corresponding with the known site of infarction and with abnormal wall motion on x-ray contrast left ventriculography. Of the 3 patients with previous non-Q-wave infarction, all had normal x-ray contrast left ventriculograms, but 1 had evidence of abnormal perfusion in the redistribution thallium images.

Magnetic resonance imaging: Twenty of the 21 patients (95%) with reversible ischemia induced by dobutamine during thallium tomography had new wall motion abnormalities similarly induced during MRI. The site of the wall motion abnormality always corresponded with the perfusion defect and was similar in extent (Figures 2 and 3). A dobutamine-induced wall motion abnormality was not detected in 1 patient with 1 segment of reversible ischemia affecting the basal inferior wall. Of the 8 patients with previous Q-wave infarction, 7 had wall motion defects at rest corresponding

with the site of infarction. The remaining patient had a small basal inferior infarction. Of the 3 patients with non-Q-wave infarction, 1 had a mild resting wall motion abnormality seen by MRI, but normal x-ray contrast left ventriculography and normal thallium images. The other 2 patients had normal resting wall motion, although 1 had a fixed thallium defect. One patient with severe 3-vessel disease and inferior infarction had both baseline inferior hypokinesis and a small area of anterior hypokinesis.

There was a significant correlation between the number of segments with wall motion defects and the extent of CAD; patients with 3-, 2-, 1- and no vessel disease had an average of 5.2 (range 4 to 7), 4.1 (0 to 6), 1.7 (1 to 3) and 3.3 (2 to 4) abnormal segments, respectively ($r_s = 0.57$; p <0.005). As with the thallium

findings, there was a wide range of defect sizes in each group, and abnormal stress wall motion was present in the 3 patients with no significant arterial stenosis.

Comparison of wall motion and perfusion: The sensitivity and specificity for the detection of individual coronary artery stenoses by thallium myocardial perfusion tomography and MRI is shown in Table III. There were no significant differences between the 2 techniques.

The numbers of patients and segments with resting abnormalities and stress-induced abnormalities of myocardial perfusion and wall motion are shown in Table IV. The similarity in the results suggests a close agreement between the techniques, whether assessed in terms of patients or segments. This was confirmed by further analysis of the differences between segmental perfusion and wall motion in the rest and stress images, and in the identification of reversible myocardial ischemia. At rest, there was agreement between techniques in 216 of 225 segments (96%), and during stress in 203 of 225 (90%).
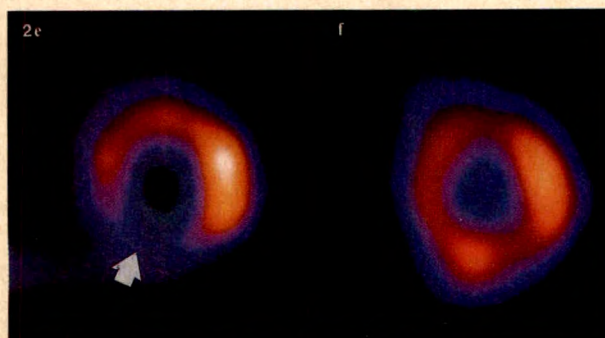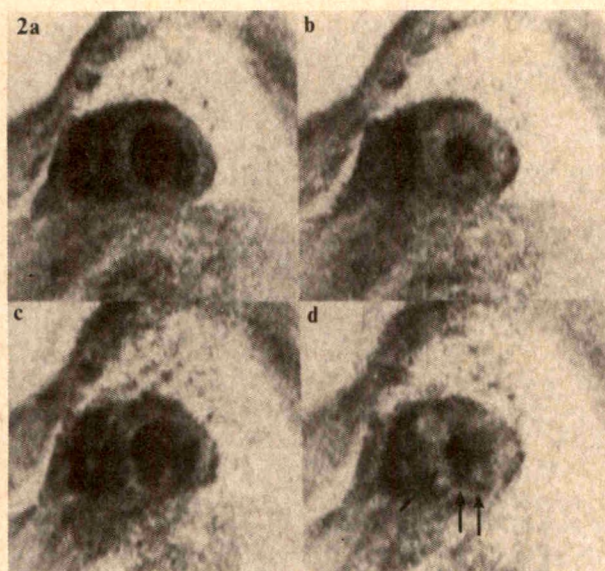
FIGURE 2. Example of inferior reversible wall motion and perfusion abnormality. Magnetic resonance images are in reverse video format, contrasting grey myocardium against black intraventricular blood. Magnetic resonance short-axis images at baseline *(a and b)* and during dobutamine stress *(c and d)*. *Left images* are at end-diastole *(a and c)*, and *right images* are at end-systole *(b and d)*. Baseline contraction pattern is normal with uniform thickening *(b)*, but during dobutamine stress *(d)*, there is abnormal contraction and thickening of inferior wall *(short arrows)* and lower septum *(long arrow)*. Corresponding thallium perfusion short-axis tomograms during stress *(e)* and after redistribution *(f)* are shown. Note reversible inferoseptal perfusion defect *(arrow)* and close correspondence with wall motion abnormality. Patient had right coronary artery disease.
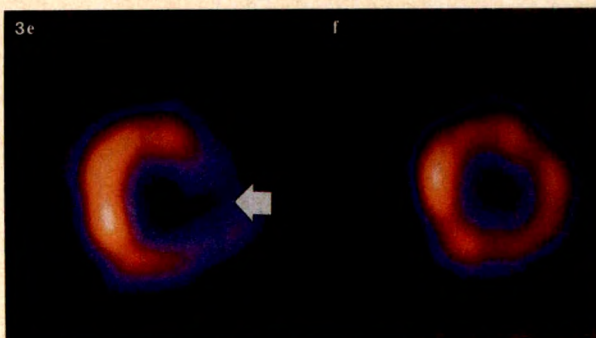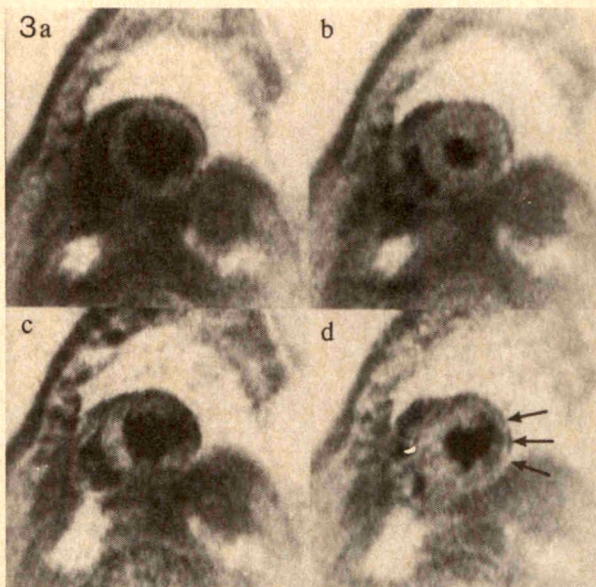
FIGURE 3. Example of lateral reversible wall motion and perfusion abnormality. Same format as Figure 2. Baseline contraction pattern is normal with uniform thickening *(b)*, but during dobutamine stress there is abnormal contraction and thickening of the lateral wall *(d, arrows)*. Corresponding thallium perfusion short-axis tomograms during stress *(e)* and after redistribution *(f)* are shown. Note reversible lateral wall perfusion defect *(arrow)* and close correspondence with wall motion abnormality. Patient had left circumflex artery disease.

TABLE III Sensitivity of Specificity of Thallium and Magnetic Resonance Imaging in the Detection of Individual Coronary Artery Stenoses

		Sensitivity (%)	Specificity (%)
Left anterior descending artery (anterior wall and septum)	Thallium	87	50
	MRI	80	50
Left circumflex artery (lateral wall)	Thallium	94	33
	MRI	94	33
Right coronary artery (inferior wall)	Thallium	85	17
	MRI	92	25
Left circumflex or right coronary artery (inferior or lateral wall)	Thallium	91	66
	MRI	91	100

MRI = magnetic resonance imaging.

TABLE IV Numbers of Patients and Myocardial Segments Classified According to the Findings of Thallium Tomography (perfusion) and Magnetic Resonance Imaging (wall motion)

	Perfusion		Wall Motion	
	Pts.	Segments	Pts.	Segments
Normal at rest	16	144	17	153
New stress abnormality	15	64	15	58
Abnormal at rest	9	13	8	14
New stress abnormality	9	24	8	19

There was agreement between techniques in 204 of 225 segments (91%) in the assessment of the presence of reversible ischemia.

Short-axis cine images had the highest contrast between blood and myocardium, and thus were the most reliable for the assessment of wall motion. However, short-axis cines are unable to assess myocardial function at the apex, and because of magnetic saturation of slow moving blood, the apex is also difficult to assess using the long-axis views; this is worsened during the tachycardia induced by dobutamine stress. This resulted in difficulty in assessing the function of the apical segment by MRI, and disagreement for this segment with thallium myocardial perfusion tomography was frequent, accounting for 9 of 22 segments where the results of the 2 techniques were disparate during stress.
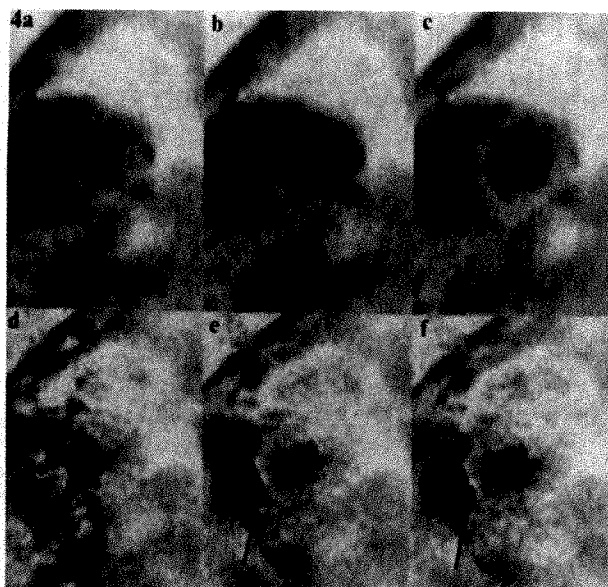
FIGURE 4. Example of reduced myocardial signal in ischemic segment. Images are in reversed video format so that signal reduction appears *white* against background *grey* myocardium. Baseline short-axis images at end-systole *(a)*, mid-diastole *(b)* and end-diastole *(c)* are shown. Images during dobutamine stress in corresponding phases of cardiac cycle *(d, e and f)* are shown. There is inferoseptal wall motion abnormality *(d, arrows)*, and during diastole, signal reduction was seen in this region *(e and f, arrows)*.

Magnetic resonance signal changes of the myocardium: In the 21 patients developing a new stress wall motion abnormality, it was possible to compare the magnetic resonance signal intensity before and after dobutamine stress in normal and ischemic areas in the short-axis plane. In normally contracting myocardium there was a small but insignificant reduction in signal, but in the ischemic myocardium there was a significant reduction (-67 units [9.2%]; $p < 0.05$). In 5 patients, the altered signal was apparent from inspection of the images (Figure 4). In 7 patients, less well-defined changes were seen. Signal reduction was most obvious during diastole.

DISCUSSION

Overall sensitivity and comparison with dipyridamole stress: We showed that MRI during dobutamine stress is feasible and relatively safe in patients with CAD. There was a 95% incidence of reversible wall motion abnormalities in patients with reversible abnormalities of myocardial perfusion, with close matching of the site and extent of the defects. Therefore, this technique may prove useful in assessment of the functional significance of CAD. These findings contrast with those from a dipyridamole MRI study in which the sensitivity was only 67%[4] and are consistent with those from dog studies comparing the 2 drugs in studies of wall motion.[13]

Sensitivity and specificity in each arterial territory: The sensitivity of the 2 techniques in the detection of individual arterial stenoses was very similar (Table III). The low specificity for both techniques in the exclusion of stenosis of the left anterior descending artery occurred because of the inclusion of 5 patients in whom significant coronary artery stenosis of the left anterior descending artery was not present, but who, however, developed perfusion and wall motion abnormalities in the anterior wall or septum (1 had a left anterior descending artery muscle bridge, 1 had 30% stenosis, and 3 were subsequently diagnosed as having syndrome X). The low specificity for both techniques in the exclusion of stenosis of the right coronary and left circumflex arteries occurred because of the difficulty in assigning a unique myocardial territory to these 2 arteries. Inferior abnormalities often develop in the presence of stenosis of either artery, whereas lateral abnormalities are unusual in right CAD.[9] Therefore, more representative figures can be determined by considering the 2 arteries together (Table III).

Comparison of magnetic resonance and thallium imaging: There were no significant differences between

MRI and thallium imaging in the diagnosis and assessment of CAD in this study, but the techniques involved are contrasting. First, stress is maintained throughout MRI, but can be stopped soon after thallium injection. Second, thallium data are obtained in 1 camera rotation and subsequently reoriented into oblique tomograms, whereas during MRI, each tomogram is obtained separately. This limits the number of tomograms that can be obtained during stress in the survey of the left ventricle. We obtained 2 long-axis and 2 short-axis slices, which allowed each segment of the ventricle to be assessed in 2 planes. Although this introduces a potential for sampling error, the results suggest that clinically significant reversible ischemia was not missed. Third, stress thallium imaging is performed after patient recovery, whereas MRI proceeds during full stress, which sometimes results in a reduction in MRI cine quality owing to increased respiratory motion. Although this did not interfere with the interpretation of the cines in these patients, this may be a problem. In response to all these difficulties, faster MRI techniques would allow a reduced period of stress, a comprehensive left ventricular survey with contiguous short-axis slices, and imaging unaffected by respiratory excursion.[1,2]

Changes in ventricular volumes with dobutamine stress: There were highly significant reductions from baseline to peak stress in end-diastolic, end-systolic and stroke volumes, and ejection fraction (Table II), but no significant correlation between the reduction of any parameter and the extent of myocardial ischemia. This suggests that the assessment of CAD using regional ventricular function during stress is more sensitive than that using global ventricular function.

Myocardial signal change: The 9.2% signal reduction observed in the myocardial segments with wall motion abnormality is of interest, because such changes have also been observed in ischemic myocardial segments using intravenous[4] and oral[14] dipyridamole. It is unlikely that the effect is the result of hypokinesis, because decreased motion should cause an increase in signal due to a reduction in motion-associated signal decrease. Acute changes in the relaxation parameters T_1 and T_2 are also an unlikely explanation, because in experimental models of ischemia, such changes are not seen until after 30 minutes.[15] Therefore, the most likely explanation is that there is a smaller increase in blood content in the abnormal myocardium during stress than in the normal myocardium.[16] Although reduced signal was seen in approximately 50% of patients with a new stress wall motion abnormality, reduced signal was occasionally seen in nonischemic areas, and therefore, the specificity of signal decrease remains to be determined.

Choice of adrenoceptor agonist: The α agonism of epinephrine and norepinephrine leads to venoconstriction if infused peripherally, and although ischemia may be provoked,[17] the need for a central infusion is not ideal. This is also true of dopamine, which has, in addition, been shown to be less effective than is dobutamine.[18] Isoprenaline has no α-agonist effects and is effective as a stressor,[19] but has no effect on blood pressure, and therefore mimics exercise less well than does dobutamine and should be administered in a central

vein because of the high acidity of its solution. Only dobutamine can be safely administered in a peripheral vein. A further advantage of dobutamine is that it is less arrhythmogenic than are other inotropes in patients with CAD.[20,21]

Effect of dobutamine: Dobutamine increases myocardial oxygen demand, and in the setting of acute ischemia has been shown to increase oxygen demand above availability.[22] It also dilates the distal coronary vessels, which leads to an increase in coronary flow,[23,24] and a decrease in perfusion pressure distal to coronary stenoses. Therefore flow becomes heterogeneous[25] and may be redirected to the subepicardium.[26] Dobutamine may also increase flow resistance at the site of a stenosis.[26]

Clinical use of dobutamine stress: Dobutamine is well-tolerated and easy to administer, and causes an increase in double product comparable with that generated by moderate levels of dynamic exercise.[27] The tachycardia also shortens imaging time. Its short action allows easy control of the stress level, it is safe in asthmatic patients, and side effects are of short duration. A disadvantage of dobutamine is that it is antagonized by β blockers, although this effect may not hinder imaging.[7] Higher doses of dobutamine may overcome β blockade, but the safety of this approach has not been established.

Study limitations: The pretest likelihood of CAD in this cohort was high, and although MRI has been shown to be feasible, extrapolation to a general population cannot be made without further studies. For the same reasons, the specificity of this technique cannot be ascertained from this study.

Images were analyzed qualitatively, and a more rigorous treatment would be desirable. Although this may be achievable for perfusion, there is no sound method available at present for wall motion analysis, particularly because ischemic wall motion can be manifest as either abnormal systolic thickening or temporal contraction heterogeneity.[28] Further development of MRI myocardial tagging may prove useful.[29]

The use of dobutamine in 1 patient was associated with improvement rather than deterioration in regional contraction in the territory of a reversible thallium perfusion defect. This effect of dobutamine has been used to identify areas of viable myocardium after myocardial infarction.[30] Further study is needed to determine if this behavior is likely to cause difficulty in the diagnosis of CAD when using dobutamine to induce regional myocardial ischemia for wall motion studies.

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Enhanced Sensitivity for Detection of Coronary Artery Disease by Addition of Atropine to Dobutamine Stress Echocardiography

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Patients undergoing dobutamine stress echocardiography often take β antagonists which limit heart rate response and sensitivity in the test for detection of coronary artery disease. The aim of this study was to assess the effect of the addition of atropine to dobutamine stress echocardiography on clinical, electrocardiographic and echocardiographic outcomes. Dobutamine stress echocardiography was performed starting at and increasing every 3 minutes with 10 μg/kg/min to a maximum of 40 μg/kg/min (stage 4), which was continued for 6 minutes. In patients not achieving 85% predicted maximal exercise heart rate and in whom the test was not judged positive on echocardiographic or electrocardiographic criteria, atropine (0.25 mg intravenously, repeated up to a maximum of 1 mg if necessary) was added and dobutamine continued for up to a further 5 minutes, or until an adequate heart rate was achieved or the test was stopped because of chest pain or electrocardiographic changes. Of 80 consecutive patients undergoing dobutamine stress echocardiography within 2 weeks of coronary angiography, 49 required atropine (group A) and 31 required only dobutamine (group B). After dobutamine alone, heart rate (mean ± SD) was higher in group B than in group A: 129 ± 20 vs 90 ± 18 beats/min, p <0.0001; but after the addition of atropine, heart rate in group A increased to 120 ± 20 beats/min. Overall sensitivity for the detection of coronary disease was 70%, 95% confidence interval (CI) 55 to 83%; after the addition of atropine, sensitivity for group A was 65%, 95% CI 45 to 81%; in group B, sensitivity was 81%, 95% CI 54 to 96%. Overall specificity for the detection of coronary disease was 88%, 95% CI 72 to 97%; specificity was 89%, 95% CI 65 to 99% after atropine in group A and 87%, 95% CI 60 to 98% in group B. The addition of atropine did not reduce specificity of the test. There were no severe complications and no difference between groups in the frequency of complications or the need to administer β blockers for relief of symptoms.

The addition of atropine to dobutamine stress echocardiography in patients whose test results are negative and who do not achieve 85% predicted maximal heart rate during dobutamine alone increases the sensitivity of the test for detection of coronary artery disease without loss of specificity and without severe adverse effects.

(Am J Cardiol 1992;70:41–46)

Stress echocardiography with exercise has a high sensitivity, specificity and reproducibility[1,2] for noninvasive detection of coronary artery disease, but requires adequate cooperation and motivation; this may be impossible in patients with orthopedic or neurologic conditions that preclude exercise. An alternative is to combine echocardiography with pharmacologic stress with dobutamine,[3] dipyridamole[4] or adenosine.[5]

Dobutamine is a sympathomimetic agent with both positive chronotropic and inotropic effects,[6] which in high doses increases myocardial oxygen demands inducing myocardial ischemia in the presence of significant coronary stenoses. Comparison of dobutamine stress echocardiography and exercise electrocardiography in patients taking β antagonists shows lower mean peak heart rate and systolic blood pressure during dobutamine than during exercise.[3] We postulated that this relatively low peak heart rate during dobutamine stress may adversely affect the sensitivity of dobutamine stress echocardiography. Accordingly, we altered the protocol for dobutamine stress echocardiography to incorporate the addition of atropine at the end of the usual dobutamine infusion in patients not achieving 85% predicted maximal exercise heart rate, and in whom the stress test was not regarded as positive during dobutamine alone. The aim of the study was to assess the effect of the addition of atropine to dobutamine on clinical, electrocardiographic and echocardiographic outcomes of the stress test, and to assess the sensitivity and specificity of this combined pharmacologic stress test for detecting coronary artery disease.

METHODS

Patient selection: Patients who received atropine in this study formed a subgroup of consecutive patients undergoing dobutamine stress echocardiography who (1) also underwent coronary angiography within 2

weeks of stress testing; (2) had negative results after dobutamine stress echocardiography with administration of dobutamine alone; and (3) did not achieve 85% predicted maximal exercise-induced heart rate for age and sex during administration of dobutamine alone.

Stress echocardiography (Figure 1): After informed verbal consent, 2-dimensional precordial echocardiography was performed at rest using Hewlett-Packard Sonos 1000 echo apparatus with 2.5 and 3.5 MHz transducers. Standard apical and parasternal views were recorded on videotape. The optimal transducer positions were marked on the chest, and a baseline 12-lead electrocardiogram was recorded. When the standard position of a chest electrode coincided with the marked transducer position the electrode was moved one space higher or lower.

After a baseline 12-lead electrocardiogram was recorded, dobutamine infusion was administered intravenously using an infusion pump, starting at a dose of 10 μg/kg/min for 3 minutes, and increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min (stage 4); this was continued for 6 minutes. In patients not achieving 85% predicted maximal exercise heart rate, atropine (0.25 mg) was given intravenously at the end of stage 4, and repeated to a maximum of 1 mg if necessary with the continuation of dobutamine for up to a further 5 minutes if necessary to achieve 85% predicted maximal exercise heart rate.

Throughout dobutamine infusion the electrocardiogram was continuously monitored, the 12-lead electrocardiogram recorded each minute and cuff blood pressure taken every 3 minutes. Two-dimensional echocardiography was continuously monitored; standard parasternal and apical images were acquired by one of the authors and were recorded on videotape for the last minute of each of stages 1 to 3, the last 4 minutes of stage 4, and continuously for up to 5 minutes after atropine administration. The infusion was stopped if the patient developed obvious new wall motion abnormality, ST depression of >2 mm 80 ms after the J point, ST elevation, significant chest pain, ventricular tachycardia, a decrease in blood pressure >20 mm Hg from resting value, or any complication considered to be due to dobutamine. Metoprolol was available and used to reverse the effects of dobutamine or atropine if these did not revert spontaneously and quickly.

Echocardiographic assessment: In addition to assessment of echo images during acquisition, additional assessment was also performed by 2 experienced investigators after acquisition. Both on- and off-line assessments were done without knowledge of the patients' coronary anatomy but with knowledge of the doses of dobutamine and atropine used. When there was disagreement between the 2 off-line assessors, a third investigator viewed the images without knowledge of the previous assessments and a majority decision was achieved. For this semiquantitative assessment, the left ventricular wall was divided into 16 segments[7] and scored using a 4-point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. An increase in score between rest and stress in 1 or more segments, i.e., a new or worsened wall motion abnormality, constituted a positive test. Using this system an index of global left ventricular wall motion (wall motion score index) was calculated as sum of the scores in the visualized segments/number of segments visualized; indexes were derived for images acquired at baseline, peak dobutamine and after atropine. In our laboratory inter- and intraobserver agreement for stress echocardiographic assessment is 91%[8]; recent data indicate that assessment of 100 stress echocardiograms is adequate training for diagnostic accuracy in this technique[9] and all investigators in our center have such experience. We do not routinely use a continuous-loop format for assessing pharmacologic stress echocardiography, because we previously tested whether cine loop analysis of dobutamine echocardiography had advantages over analysis of images from videotape and found the same results with the 2 techniques.[3]

Coronary angiography: Coronary angiography was performed by the Judkins' technique within 2 weeks of stress echocardiography. A lesion of >50% diameter stenosis is taken as representing significant coronary artery disease. The decision to perform coronary angiography was never based on the results of stress echocardiography.

Statistical analysis: Results are expressed as mean ± SD and 95% confidence intervals (CI) are given where appropriate. Discrete variables were compared using the chi-square test or Fisher's exact test; continuous variables were compared using paired and unpaired Student's t tests or 1-way analysis of variance as appropriate.

RESULTS

Study population: Eighty consecutive patients undergoing dobutamine stress echocardiography and coronary angiography were included in the study. Clinical details are summarized in Table I. Forty-nine patients received atropine in addition to dobutamine (group A) and 31 achieved a test end point with dobutamine alone (group B). There was no difference between these 2 groups with regard to the overall incidence of significant coronary artery disease, but there was a trend toward more 1-vessel disease in group A: 24 of 31 (77%) pa-
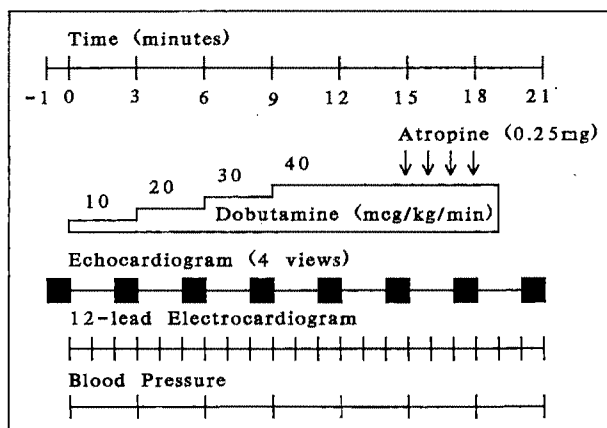
FIGURE 1. Schematic representation of the study protocol.

TABLE I Clinical Characteristics of Patients Receiving Atropine (group A) and No Atropine (group B)

	Group A	Group B	p Value
No. of patients	49	31	
Men:women	40:9	19:12	0.08
Mean age ± SD	57 ± 12	62 ± 10	0.05
Coronary artery disease	31 (63%)	16 (52%)	NS
1 vessel:multivessel	24:7	8:8	0.11
LAD:LC:right	21:12:7	8:5:11	0.05
Previous MI	19 (39%)	9 (29%)	NS
Previous PTCA	24 (49%)	15 (48%)	NS
Previous CABG	2 (4%)	2 (7%)	NS
β antagonists	46 (94%)	18 (58%)	0.0003
Calcium antagonists	29 (59%)	15 (48%)	NS
Nitrates	20 (41%)	13 (42%)	NS

CABG = coronary artery bypass grafting; LAD = left anterior descending; LC = left circumflex; NS = not statistically significant; PTCA = percutaneous transluminal coronary angioplasty.

TABLE II Frequency of Primary Reasons for Stopping Stress Test

	Group A	Group B
No. of patients	49	31
Adequate heart rate	30 (61%)	19 (61%)
Chest pain	12 (25%)	7 (23%)
ST elevation	2 (4%)	4 (13%)
ST depression	3 (6%)	0
New wall motion abnormality	0	1 (3%)
Chills	2 (4%)	0

TABLE III Changes in Heart Rate After Dobutamine and Atropine

	Base	Peak Dobutamine	Peak Atropine	p Value
Group A (all)	64 ± 9.6	90 ± 18.4	120 ± 19.6	<0.0001
(+CAD)	63 ± 9.8	88 ± 18.7	118 ± 19.0	<0.0001
(−CAD)	66 ± 9.7	92 ± 18.3	122 ± 20.0	<0.0001
Group B (all)	76 ± 13.6	129 ± 20.1	—	<0.0001
(+CAD)	74 ± 14.6	128 ± 21.4	—	<0.0001
(−CAD)	77 ± 12.8	130 ± 19.3	—	<0.0001

Analysis in group A was performed by 1-way analysis of variance and in group B by paired t tests.
+CAD = patients with significant coronary artery disease; −CAD = patients without significant coronary artery disease.

TABLE IV Changes in Systolic Blood Pressure After Dobutamine and Atropine

	Base	Peak Dobutamine	Peak Atropine	p Value
Group A (all)	129 ± 17	139 ± 19	147 ± 24	<0.0001
(+CAD)	127 ± 16	140 ± 19	149 ± 25	0.0003
(−CAD)	131 ± 19	139 ± 18	142 ± 23	0.25
Group B (all)	136 ± 22	148 ± 30	—	0.001
(+CAD)	142 ± 25	154 ± 33	—	0.03
(−CAD)	130 ± 17	141 ± 25	—	0.01

Explanation and abbreviations as in Table III.

tients with coronary disease in group A had 1-vessel disease compared with 8 of 16 (50%) in group B, p = 0.11. The distribution of diseased vessels was different between the 2 groups, with a greater proportion of patients from group A having left anterior descending and circumflex lesions and more patients in group B having right coronary lesions. Mean age was lower and β antagonist use was more frequent in group A. There was no difference between groups in the frequency of previous infarction, angioplasty or coronary artery bypass grafting.

Reasons for termination of the test: The primary reasons for termination of the stress test in the 2 groups are listed in Table II. In some cases a patient had an additional reason for stopping, e.g., chest pain accompanying ST elevation. There was no difference between groups in the reasons for termination of the test; in >60% of patients from both groups, the test was discontinued primarily because an adequate heart rate was achieved. In only 1 patient was the test stopped because of new wall motion abnormality.

Hemodynamic changes: Changes in heart rate and systolic blood pressure with dobutamine and atropine are shown in Tables III and IV. In group A, both heart rate and systolic blood pressure increased significantly after dobutamine alone and increased further after addition of atropine. Within group A there was no difference between patients with and without coronary artery disease for either mean heart rate or systolic blood pres-

sure at baseline, after dobutamine or after addition of atropine. In group B, mean heart rate and systolic blood pressure increased significantly from baseline to peak dobutamine, and there was no difference between those with and without coronary artery disease for values at base and peak stress.

Comparison of heart rate data between groups A and B showed a higher baseline value in group B: 76 ± 13.6 beats/min compared with 64 ± 9.6 beats/min, p <0.0001. At peak dobutamine, heart rate in group A was 90 ± 18.4 beats/min compared with 129 ± 20.1 beats/min in group B, p <0.0001. There was a small difference between peak stress (peak atropine in group A, peak dobutamine in group B) heart rates in the 2 groups: 120 ± 19.6 beats/min for group A and 129 ± 20.1 beats/min for group B, p = 0.04.

Base and peak dobutamine systolic blood pressures tended to be higher in group B although the differences did not reach statistical significance: 129 ± 17 mm Hg compared with 136 ± 22 mm Hg, p = 0.09 for baseline values; and 139 ± 19 mm Hg compared with 148 ± 30 mm Hg, p = 0.13 for peak dobutamine. There was no difference between groups A and B for peak stress systolic blood pressure: 147 ± 24 and 148 ± 30 mm Hg, p = 0.86.

Sensitivity and specificity of stress echocardiography: Of the 47 patients with significant coronary artery disease, 33 developed a new or worsened wall motion abnormality in the area of myocardium judged to be subtended by the stenotic coronary artery after either dobutamine or atropine (an overall sensitivity of 70%, 95% CI 55 to 83%). In group A, off-line review revealed new wall motion abnormalities, which had been unrecognized during on-line assessment in 2 of 31 patients

(7%, 95% CI 1 to 21%) with coronary artery disease before the addition of atropine; 20 of 31 had new wall motion abnormalities after the addition of atropine (sensitivity for group A of 65%, 95% CI 45 to 81%). In group B, new or worsened wall motion abnormalities occurred in 13 of 16 patients with coronary artery disease (sensitivity 81%, 95% CI 54 to 96%) (Figure 2).

The overall specificity of stress echocardiography for detection of coronary artery disease was 88%, 95% CI 72 to 97% (4 of 33 patients without significant coronary disease developed a new or worsened wall motion abnormality after either dobutamine or atropine). In group A, none of the 18 patients without coronary disease had a positive echocardiographic finding with dobutamine alone, but in 2 patients the echocardiogram became positive after the addition of atropine (specificity 89%, 95% CI 65 to 99%). In group B, 2 of the 15 patients without coronary disease had a positive echocardiographic results after dobutamine (specificity 87%, 95% CI 60 to 98%) (Figure 3). Of the 49 patients in group A, 4 had wall motion abnormalities at rest, which worsened in 2 during atropine administration and remained unchanged in 2. In the other 45 patients with normal

wall motion at rest, 2 had new wall motion abnormalities after dobutamine alone and 18 when atropine was added. In group B, 12 had wall motion abnormalities at rest. Of them, 9 had new or worsened wall motion abnormalities. In the other patients in group B, 19 had a normal wall motion at rest, which became abnormal in 6.

Sensitivity and specificity of ST changes and chest pain: Sensitivities of ST changes and chest pain induced by dobutamine or atropine as indicators of coronary artery disease are also shown in Figure 1. In group A, 2 of 31 patients (7%, 95% CI 1 to 21%) with coronary disease had ST depression of 1 mm 80 ms after the J point during dobutamine therapy alone, whereas 6 (19%, 95% CI 8 to 38%) had ST changes (4 depression, 2 elevation) after the addition of atropine. In group B, 7 of 16 patients (44%, 95% CI 20 to 70%) with coronary disease had ST changes (4 elevation) during administration of dobutamine. In the 6 studies that resulted in ST elevation, this quickly resolved on termination of the stress test and administration of intravenous metoprolol. Three of these patients had previous infarction and 1 had a totally blocked right coronary artery despite no
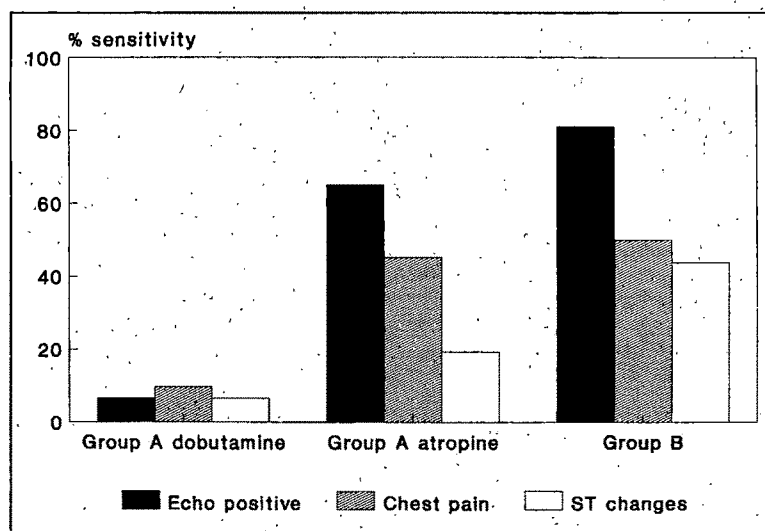
FIGURE 2. Sensitivity of echocardiography (Echo), chest pain and ST-segment changes for detection of coronary artery disease. Group A atropine = sensitivities after addition of atropine; Group A dobutamine = sensitivities in group A before addition of atropine.
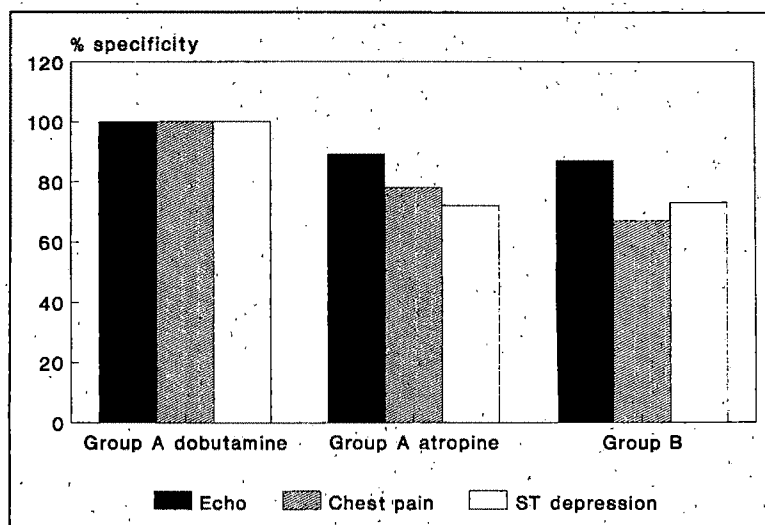
FIGURE 3. Specificity of echocardiography (Echo), chest pain and ST depression for detection of coronary artery disease. Group A atropine = specificities after addition of atropine; Group A dobutamine = specificities in group A before addition of atropine.

history of infarction; 3 had multivessel and 3 single-vessel disease.

Of 31 patients with coronary artery disease in group A, chest pain occurred in 3 (10%, 95% CI 2 to 26%) during dobutamine alone, and in 14 (45%, 95% CI 27 to 64%) after the addition of atropine. In group B, 8 of 16 patients (50%, 95% CI 25 to 75%) with coronary artery disease had chest pain during dobutamine therapy.

Specificities of dobutamine- and atropine-induced ST-segment changes and chest pain for detection of coronary artery disease are shown in Figure 2. There was no ST depression or chest pain in the 18 patients without coronary disease in group A during dobutamine therapy alone, but ST depression occurred in 5 patients (specificity 72%, 95% CI 47 to 90%) and chest pain in 4 (specificity 78%, 95% CI 52 to 94%) after the addition of atropine. In group B, 4 of the 15 patients without coronary disease developed ST depression during dobutamine therapy (specificity 73%, 95% CI 45 to 92%), and 5 experienced chest pain (specificity 67%, 95% CI 38 to 88%).

Wall motion score indexes: There was no change in mean wall motion score index between rest and peak dobutamine (1.04 ± 0.13 compared with 1.06 ± 0.14, p = 0.21) in patients with coronary artery disease from group A, but there was a significant increase in mean wall motion score index between peak dobutamine and peak atropine (1.06 ± 0.14 to 1.17 ± 0.15), p <0.0001. Mean wall motion score index for patients with coronary artery disease in group B increased from 1.29 ± 0.42 at baseline to 1.52 ± 0.43 after dobutamine, p <0.0001. There was no change in wall motion score index for patients without coronary disease in either group A or group B.

Complications: There were no serious complications related to either dobutamine or atropine. One or more minor side effects occurred at peak stress in 15 patients from group A (31%) and 13 patients (42%) from group B (Table V); 11 patients (23%) from group A and 12 (39%) from group B required intravenous metoprolol after peak stress, usually for relief of chest pain that did not settle quickly and spontaneously. There was no significant difference between groups in the incidence of adverse effects or requirement for metoprolol (Table V).

DISCUSSION

Study rationale: Patients undergoing noninvasive cardiac investigations at our institution are often receiving β antagonists[3,8] for suspected angina, after infarction or for hypertension, and withdrawal of medication may be impractical or even potentially hazardous. Dobutamine has β-stimulant properties[7] that result mainly in increased inotropic and, to a lesser extent, increased chronotropic effects that are reduced in patients using β blockers. We postulated that this may limit the sensitivity of dobutamine stress testing for detection of coronary artery disease in these patients. Our suspicions were supported by data from other centers that showed a high incidence of electrocardiographic changes[10,11] during dobutamine infusion in patients with coronary

TABLE V Side Effects at Peak Stress During Dobutamine or Atropine		
	Group A	Group B
Continuing chest pain	10	11
Ventricular tachycardia (3 beats)	2	1
Atrial ectopics	1	0
Nodal rhythm	1	0
Chills	2	0
Headache	1	0
Dyspnea	0	1

disease who were not taking β antagonists, and by recent data that indicate that antianginal therapy including β blockade limits the sensitivity of dipyridamole echocardiography.[12]

The negative chronotropic effect of β antagonists can be overcome by atrial pacing, which is an alternative nonexercise stress; however, even by the esophageal route[13] this requires adequate patient cooperation and suitable pacing electrodes and has no effect on inotropic action. Therefore, to retain the inotropic effect of dobutamine, but to overcome the lack of chronotropic effect seen especially in patients receiving β antagonists, we combined dobutamine stress echocardiography with atropine to increase heart rate[14] in patients with negative stress echocardiography who did not achieve 85% predicted maximal exercise-induced heart rate with dobutamine alone. We compared the results of this combined stress test with those seen in the same patients after dobutamine alone, and with the outcome of stress echocardiography in consecutive patients undergoing dobutamine stress testing without the requirement for atropine, during the same time period as those who received atropine.

Stress echocardiography: sensitivity, specificity, and wall motion score index: In accordance with the protocol, no patient with a positive echocardiogram during dobutamine therapy alone should have received atropine. However off-line review revealed minor new wall motion abnormalities that had not been detected on-line before the addition of atropine to 2 patients from group A. The sensitivity for detecting coronary lesions with >50% diameter stenosis was 65% for patients in group A and 81% for those in group B, resulting in an overall sensitivity of 70%, with very similar CIs for groups A and B; this similar sensitivity was achieved despite a tendency toward more multivessel disease in group B, a factor which we have previously shown to increase positivity of dobutamine stress echocardiography.[3] Had these patients been studied using our former protocol, stopping after 15 minutes of dobutamine infusion regardless of heart rate, 15 of the 47 patients with coronary disease would have had a positive echocardiogram, resulting in a significantly lower sensitivity of 32%, 95% CI 19 to 47%.

The overall sensitivity for detection of coronary disease of 70% with a 95% CI of 55 to 83% is slightly lower but comparable to that reported for tomographic thallium scintigraphy after exercise[5] or pharmacologic stress with adenosine[5] or dipyridamole[15]; however, our

study of patients with predominantly 1-vessel disease cannot be directly compared with other studies in which a greater proportion of patients had multivessel disease. In addition, stress echocardiography has the advantage of requiring only readily available equipment compared with that required for perfusion scintigraphy, and avoids the exposure to a radioisotope.

In this study we did not use the side-by-side analysis of rest- and stress-digitized image. However, it is unlikely that this could explain the relatively low sensitivity of the test, as we have recently reported.[3]

The increased sensitivity as a result of adding atropine was associated with only a small reduction in specificity; after dobutamine alone 31 of the 33 patients without coronary disease had a negative echocardiographic response (specificity 94%, 95% CI 80 to 99%) compared with 29 of 33 (specificity 88%, 95% CI 72 to 97%) after the addition of atropine.

The effect of atropine in increasing diagnostic yield is also reflected by the changes in wall motion score index seen in group A. For patients with coronary artery disease in group A there was no significant increase in wall motion score index after dobutamine alone, but a significant increase after the addition of atropine. However in accordance with the lack of effect of atropine on specificity, wall motion score index did not increase after the administration of atropine in patients without coronary disease. Similarly, in group B, there was an increase in wall motion score index at peak stress in patients with coronary disease, but no increase in those without coronary disease.

Safety of the combined stress test: There were no severe side effects at peak dobutamine or atropine infusion, and no difference between the incidence of side effects between groups A and B. In particular, the requirement for metoprolol was the same between the 2 groups. This was usually given for chest pain that did not resolve within 5 minutes of stopping dobutamine. In patients who developed ST elevation, metoprolol was immediately given and resulted in rapid resolution of ST elevation and chest pain in all cases. Although there were no severe arrhythmias (2 patients had 3 beats of ventricular tachycardia at peak stress, and 1 patient developed nodal rhythm with maintainance of normal blood pressure), the test should only be performed with attention to electrocardiographic monitoring, 12-lead ST-segment assessment and blood pressure recording, and with resuscitation facilities available.

Relation to other studies: Recent studies of dobutamine echocardiography have reported sensitivities of 86 to 89% for detection of coronary disease.[16,17] These sensitivities are outside the 95% confidence limits for sensitivity in our study, but there are several important differences between these studies and ours. Cohen et al[16] reported an overall sensitivity of 86%, but their patients were studied without β blockade, and 16 of 51 patients with significant coronary disease had 1-vessel disease, for whom sensitivity was 69%, whereas sensitivity for patients with multivessel disease was 94% (33 of 35 pa-

tients). Sawada et al[17] reported a sensitivity of 89%, but only a small amount of patients were taking β blockers and only patients with normal resting echocardiograms were considered in this analysis. Our overall sensitivity of 70% and the sensitivity of 93% for multivessel disease is comparable with the sensitivity of other imaging techniques including tomographic thallium imaging after exercise[5,18] or pharmacologic stress with adenosine[5] or dipyridamole.[19]

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Initial Management and Long-Term Clinical Outcome of Restenosis After Initially Successful Percutaneous Transluminal Coronary Angioplasty

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Restenosis remains a critical limitation after percutaneous transluminal coronary angioplasty (PTCA). The clinical experience with restenosis was reviewed in 1,490 patients who had restenosis of at least 1 site within 1 year of their PTCA. The source of data was the clinical database at Emory University. Patients who had previous coronary bypass surgery or PTCA and patients who underwent PTCA in the setting of acute myocardial infarction were excluded. When restenosis was angiographically documented, 363 were treated medically, 1,051 with repeat PTCA, and 76 with coronary bypass surgery. In the repeat PTCA group there were 778 patients who originally had 1-vessel disease and 273 with multiple vessel disease. Re-dilatation of restenotic sites was performed in 95%. Angiographic success of all lesions dilated was achieved in 99%. Coronary bypass surgery was required in 2.5% of patients with restenosis first treated with repeat PTCA. One patient with multiple vessel disease died. Coronary bypass surgery was performed in fewer patients aged ≥65 years, but more patients with multiple vessel disease. Two (2.6%) of the coronary bypass surgery patients had Q-wave myocardial infarction and there were no deaths. In the PTCA group, 5-year actuarial survival was 95%, and cardiac survival 96%. Freedom from cardiac events or further revascularization procedures was 51% at 5 years. Patients treated with PTCA and medically treated patients had similar cardiac survival rates. The most important correlates of cardiac survival were age and the presence of diabetes mellitus. At 5 years, cardiac survival without diabetes was 97 and 83% with diabetes (p <0.0001). Selection of the appropriate form of therapy for restenosis cannot be easily determined from grouped data, but rather requires patient by patient selection. In patients with restenosis, with careful selection of therapy, excellent results may be obtained with low initial morbidity and mortality and high long-term survival.

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Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977, much has been learned about the procedure including the primary success rate, the dangers of acute complications of myocardial infarction, the need for emergent coronary bypass surgery and death.[1-5] The frequency of restenosis, and to some extent risk factors for restenosis, have been defined.[6,7] There are also data regarding the re-dilation of stenotic lesions.[8-12] However, little is known about the impact of restenosis on subsequent medical care and long-term prognosis. This study surveys the treatment strategies and the long-term course of patients with restenosis.

METHODS

Patient population: From June 1980 through December 1988, 7,561 patients without prior PTCA or coronary bypass surgery underwent elective PTCA performed at Emory University or Crawford W. Long Hospitals. Included in this analysis were patients who had the procedure performed electively for stable or unstable angina pectoris or after several days of stabilization after acute myocardial infarction. Those who underwent the procedure acutely in the setting of a myocardial infarction or after cardiopulmonary resuscitation for cardiac arrest were excluded. Of the total, 6,925 patients had an angiographically successful procedure and did not have complications of a Q-wave myocardial infarction, the need for in-hospital coronary bypass surgery or death. Patients returned for restudy after PTCA either to determine whether restenosis has occurred, or because of recurrent symptoms. From this population of initially successful patients, 3,056 patients had an angiographic restudy (44%). Of this group, 1,490 patients were found to have restenosis of at least 1 of their dilated lesions and form the population for this study.

Definitions: ONE-VESSEL DISEASE: ≥50% diameter luminal narrowing in either the left anterior descending, left circumflex, or right coronary or a major branch or branches.

TABLE I Clinical Characteristics by Mode of Therapy

	Total n (%)	Medical Therapy n (%)	Repeat PTCA n (%)	Coronary Surgery n (%)	p Value
Patients	1,490	363	1,051	76	
Time from original PTCA (days)	153 ± 73	182 ± 70	143 ± 71	142 ± 79	<0.0001
<60 days from PTCA	125 (8.4)	16 (4.4)	102 (9.7)	7 (9.2)	0.0070
Age (years)	57 ± 10	57 ± 10	57 ± 10	57 ± 8	NS
≥65 years	299 (20)	87 (24)	202 (19)	10 (13)	.0.046
Male gender	1,172 (79)	268 (74)	841 (80)	63 (83)	0.03
Prior myocardial infarction	452 (31)	140 (39)	289 (28)	23 (31)	0.0003
Systemic hypertension	641 (43)	145 (39)	465 (44)	31 (41)	NS
Diabetes mellitus	185 (12)	39 (11)	135 (13)	11 (14)	NS
Asymptomatic at restudy	129 (12)	36 (27)	92 (10)	1 (1.8)	<0.0001
Grade I–II angina at restudy	431 (40)	43 (32)	360 (40)	28 (49)	
Grade III–IV angina at restudy	524 (48)	55 (41)	441 (49)	28 (49)	
	(n = 1,084)	(n = 134)	(n = 893)	(n = 57)	

NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

TABLE II Original Angiographic and Procedural Characteristics by Mode of Therapy

	Total n (%)	Medical Therapy n (%)	Repeat PTCA n (%)	Coronary Surgery n (%)	p Value
Originally multiple vessel disease	414 (28)	110 (30)	273 (26)	31 (41)	0.0097
Original ejection fraction	59 ± 11	57 ± 12	60 ± 11	61 ± 11	0.0009
Ejection fraction <50%	138 (15)	43 (21)	90 (14)	5 (9.4)	0.014
	(n = 911)	(n = 201)	(n = 657)	(n = 53)	
Total occlusion dilatation	104 (7.0)	35 (9.6)	62 (5.9)	7 (9.2)	0.040
Left anterior descending dilatation	936 (63)	204 (56)	680 (65)	52 (68)	0.009
Originally multiple site dilatation	395 (26)	122 (34)	245 (23)	28 (37)	0.0001
Diameter stenosis pre-PTCA	75 ± 15	75 ± 14	75 ± 14	76 ± 15	NS
Diameter stenosis post-PTCA	25 ± 11	25 ± 11	25 ± 10	26 ± 11	NS
Lesion length (mm)	6.8 ± 4.4	7.0 ± 4.6	6.6 ± 4.2	7.3 ± 5.4	NS
Lesion length >15.0 mm	67 (4.7)	22 (6.3)	39 (3.9)	6 (8.2)	0.06

Abbreviations as in Table I.

MULTIPLE VESSEL DISEASE: the presence of ≥50% diameter luminal narrowing in >1 of these major epicardial vessel systems.

ANGIOGRAPHICALLY SUCCESSFUL PTCA: all lesions attempted improved ≥20% diameter stenosis and were dilated to <50% residual diameter stenosis.

CLINICALLY SUCCESSFUL PTCA: angiographically successful PTCA without the complications of Q wave myocardial infarction, coronary bypass surgery or death.

RESTENOSIS: recurrent diameter narrowing of ≥50% of any site dilated.

Data collection: Baseline and restudy demographic, clinical, angiographic and procedural data including complications were recorded prospectively by physicians on standardized forms and entered into a computerized data base. The pre-PTCA, post-PTCA and restudy angiograms were measured with validated digital electronic calipers (Sandhill Scientific Inc., Littleton, Colorado after 1983, with a prototype 1981 to 1983)[13] or by hand tracing (1980 to 1981) by experienced angiographers other than the primary operator. The narrowing of each coronary artery lesion was expressed as the percent diameter narrowing of the abnormal segment compared with the normal adjacent arterial regions. The diameter stenosis recorded was the mean value determined in 2 near orthogonal views.

Percutaneous transluminal coronary angioplasty technique and angiographic restudy: All PTCA procedures were performed using standard techniques which have previously been described.[14] Restudy angiography after PTCA was performed under the guidance of the primary PTCA operator. While the entire coronary tree was visualized, special attention was directed at the original dilatation sites. Assessment of the severity of obstruction of these sites was specifically addressed and recorded.

Patient follow-up: Follow-up information was obtained by telephone interviews of the patients, referring physicians or medical records. All follow-up contacts are performed by trained personnel. Follow-up information included occurrence of myocardial infarction since the initial PTCA, subsequent need for an additional revascularization procedure (PTCA or coronary bypass surgery) or death (cardiac or noncardiac). All follow-up information was recorded on standardized forms and entered into the computerized data base. In addition, all events noted on forms entered into the database from hospitalizations after the restudy angiogram were included. Follow-up after the angiographic restudy was 99% complete. The accuracy of these methods of follow-up for death have been verified against the state of Georgia death tapes. Additional revascularization procedures are likely to be similarly complete because the

TABLE III Angiographic and Dilatation Site Characteristics at Restudy

	Total n (%)	Medical Therapy n (%)	Repeat PTCA n (%)	Coronary Surgery n (%)	p Value
Restudy multiple vessel disease	408 (28) (n = 1,437)	106 (34) (n = 313)	262 (25) (n = 1,051)	40 (55) (n = 73)	<0.0001
Restudy ejection fraction	60 ± 11 (n = 821)	59 ± 12 (n = 222)	61 ± 10 (n = 544)	59 ± 11 (n = 55)	NS
Diameter stenosis at restudy (most severe site)	74 ± 19	72 ± 19	74 ± 13	80 ± 14	<0.0001
≥ 1 site totally occluded	138 (9.3)	75 (21)	50 (4.8)	13 (17)	<0.0001
All sites <60% occluded	316 (21)	151 (42)	159 (15)	6 (7.9)	<0.0001
Left anterior descending restenosis	911 (61)	189 (52)	672 (64)	50 (66)	0.0002
Circumflex restenosis	236 (16)	58 (16)	164 (16)	14 (18)	NS
Right coronary artery restenosis	392 (16)	123 (34)	250 (24)	19 (25)	0.0008
Multiple sites restenotic	173 (12)	43 (12)	111 (10)	19 (25)	

Abbreviations as in Table I.

events are recorded in the data base as they occur. Myocardial infarctions occurring after the patient is discharged will always be more uncertain, with potential for both under- and over-reporting.

Statistical analyses: Differences in categoric variables were analyzed by chi-square and differences in continuous variables were analyzed by Student's t tests or 1-way analysis of variance where appropriate. The patients were divided by the treatment received at the time of restudy: medical therapy, repeat PTCA or coronary bypass surgery. The clinical, angiographic and procedural characteristics of each group were determined. Correlates of a second episode of restenosis were determined by stepwise logistic regression analysis. Overall survival and event-free survival were determined by the Kaplan-Meier method[15] and probability was expressed as the mean ± standard error of the estimate. Overall survival and event-free survival were determined for the total population, as well as the subgroups. End points analyzed included: (1) cardiac survival; (2) freedom from cardiac death or myocardial infarction; (3) freedom from cardiac death, myocardial infarction or coronary bypass surgery; and (4) freedom from cardiac death, myocardial infarction, coronary bypass surgery or repeat PTCA. Comparisons of total and event-free survival were made using the Mantel-Cox method.[16] Correlates of late events were determined by the Cox proportional hazards model.[17] For Cox model analyses, continuous covariates were not broken into groups. All statistical analyses were performed with BMDP statistical software (Los Angeles, California).

RESULTS

This study concerns 1,490 patients who underwent successful, uncomplicated PTCA, followed by restenosis of at least 1 site on angiographic restudy. Clinical characteristics, grouped by the treatment method selected after restenosis was documented, are presented in Table I. These 1,490 patients were treated as follows: 363 (24%) were treated medically, without initial repeat revascularization by PTCA or coronary bypass surgery, 1,051 (70%) underwent repeat PTCA, and only 76 (5.1%) had coronary bypass surgery without an attempted repeat PTCA. The patients selected for medi-

cal therapy were those in whom repeat PTCA or coronary bypass surgery was considered unnecessary. The time from initial PTCA to restudy was slightly longer in the medically treated patients. There was no difference in mean age, although the percentage of patients aged ≥65 years was highest in the medically treated patients, lower in the PTCA patients, and lowest in the coronary bypass surgery patients. There were more women in the medically treated than PTCA or coronary bypass surgery groups. There was no significant difference in the incidence of diabetes. Asymptomatic status was most often noted in the medically treated patients and was rare in the patients sent to coronary bypass surgery. Class III to IV angina was noted in 48% of patients at restudy, compared with 60% before the original PTCA.

Angiographic and procedural characteristics from the original procedure are presented for the 3 treatment arms in Table II. Multiple vessel disease was noted most often in the coronary bypass surgery patients (41%) and least often in the PTCA patients (26%). The ejection fraction was slightly lower and a larger proportion had ejection fractions <50 in the medically treated patients. Patients who originally had total occlusion dilations were somewhat less likely to have repeat dilations. Medically treated patients were least likely to have had left anterior descending coronary artery dilatations. Multiple site dilatations were least common in the group that subsequently underwent repeat PTCA. The lesion severity and length varied little between the subsequent treatment groups. The data presented are for the first site dilated during a hospitalization. The data for subsequently dilated sites are similar.

The angiographic and dilatation site characteristics at restudy are displayed in Table III. Patients undergoing coronary bypass surgery were most likely to have multiple vessel disease, although only 10% of patients with multiple vessel disease underwent coronary bypass surgery. The ejection fraction did not vary between groups. The most severely obstructed site averaged 74 ± 19% stenosis. The mean obstruction was lowest in the medically treated patients, mid often in the PTCA patients, and highest in the coronary bypass surgery group. Totally occluded sites were less common in the PTCA group, but were more common in the groups

TABLE IV Results of Repeat PTCA After Documented Restenosis

	Total n (%)	1-Vessel Disease n (%)	Multiple Vessel Disease n (%)	p Value
Patients	1,051	789	262	
Redilations of stenotic sites	1,000 (95)	761 (96)	239 (91)	0.0006
Multiple site dilatation	178 (17)	91 (12)	87 (33)	<0.0001
Left anterior descending dilatation	667 (64)	530 (67)	137 (52)	<0.0001
Diameter stenosis pre-PTCA	72 ± 13	71 ± 13	73 ± 13	0.02
Diameter stenosis post-PTCA	27 ± 15	26 ± 14	29 ± 17	0.036
Angiographic success	1,036 (99)	780 (98)	256 (98)	0.066
Q-wave myocardial infarction	8 (0.8)	3 (0.4)	5 (1.9)	0.014
Coronary surgery	26 (2.5)	15 (1.9)	11 (4.2)	0.038
Death	1 (0.1)	0 (0)	1 (0.4)	0.08
Clinical success	1,008 (96)	764 (97)	244 (93)	0.0089
Angiographic rerestudy after repeat PTCA	422	307	115	
Restenosis present	213 (51)	149 (48)	64 (55)	NS
Most severe stenosis at rerestudy	51 ± 27	49 ± 27	54 ± 27	0.080

Abbreviations as in Table I.

TABLE V Correlates of Second Restenosis

	No Restenosis	Restenosis	Relative Risk	Univariate p Value	Multivariate p Value	Coefficient
Pre-PTCA diameter stenosis <70%	96 (62)	59 (38)	1	<0.0001	<0.0001	−0.0340
Pre-PTCA diameter stenosis 70–99%	113 (45)	140 (55)	1.45			
Pre-PTCA diameter stenosis 100%	2 (22)	7 (78)	2.04			
First PTCA to restudy <150 days	110 (45)	136 (55)	1.76	<0.0001	<0.0001	0.00791
First PTCA to restudy ≥150 days	102 (68)	47 (32)	1			
Diabetes mellitus absent	198 (54)	172 (46)	1	0.0008	0.004	−0.502
Diabetes mellitus present	14 (29)	34 (71)	1.52			
Post-PTCA diameter stenosis <30	141 (56)	111 (44)	1	0.056	NS	
Post-PTCA diameter stenosis ≥30	69 (44)	89 (56)	1.28			
Age <65 years	183 (53)	164 (47)	1	0.067	NS	
Age ≥65 years	29 (41)	42 (59)	1.25			
Constant						1.15

Abbreviations as in Table I.

treated with medical therapy or coronary bypass surgery. Patients with milder restenosis (all sites <60% occluded) tended to be treated medically. The percentage of patients with all sites <60% occluded was 42% for the medically treated but just 7.9% in the coronary bypass surgery group. Patients who had coronary bypass surgery had a higher percentage of multiple restenotic sites; in these patients, 2 (3.3%) had Q-wave myocardial infarctions and none died in the hospital.

The results of repeat PTCA are presented in detail in Table IV. The patients are classified into those with 1- and multiple vessel disease on the restudy angiogram. Of the 1,051 patients undergoing repeat PTCA, 789 (75%) had 1-vessel disease and 262 (25%) had multiple vessel disease. The overwhelming majority (95%) had repeat dilation of at least 1 restenotic site, with the remainder having PTCA at new sites. Multiple vessel dilatations were relatively infrequent, although performed more often in the patients with multiple vessel disease. The left anterior descending artery was dilated more often in patients with 1-vessel disease. The PTCA angiographic results refer to the repeat PTCA. Angiographic success was achieved in the overwhelming majority of cases (99%). One patient in the multiple vessel group died. Coronary bypass surgery and the incidence of a Q-wave infarction were noted more frequently in patients with multiple vessel disease. Clinical success was achieved in 96%, and was higher in those with 1-vessel disease. Clinical success was achieved in 965 of the 1,000 patients having repeat dilatations (96%). Of these 965, 422 (44%) had a second restudy coronary arteriograms after repeat PTCA. Approximately half the patients had restenosis at at least 1 site undergoing repeat dilatation, although the low restudy rate limits the ability to determine the rate of a second episode of restenosis.

The correlates of a second episode of restenosis are presented in Table V. The univariate and multivariate correlates of a second episode of restenosis are the diameter stenosis before the second PTCA, with more severe stenoses and total occlusions more likely to restenose again, a shorter period of time from the first PTCA to restenosis, and the presence of diabetes mellitus. This model may be influenced somewhat by the restudy rate of 44%. Multivariate analysis was used to create nomograms to predict the probability of a second

episode of restenosis. Figure 1 (top) shows patients without diabetes and Figure 1 (bottom) patients with diabetes. Curves are presented for diameter stenoses of 50 to 100% at the time of the second PTCA. These curves permit the assessment of restenosis risk from variables that are continuous. As the time from first PTCA to restenosis increases, the risk of recurrent restenosis decreases. Similarly, as the severity of the restenotic lesions decreases, the risk of recurrent restenosis decreases. The risk of recurrent restenosis is also higher in diabetic patients.

Long-term prognosis after a diagnosis of restenosis is described in the following figures and tables. In Figure 2 the overall prognosis is displayed. The 4 curves are cardiac survival, myocardial infarction free survival, freedom from death, myocardial infarction, coronary bypass surgery or PTCA. The overall actuarial survival at 5 years was 95%, quite close to the cardiac survival of 96%. As most of the patients had repeat dilatations, the event-free survival decreases to a very low level quite rapidly. However, the cardiac survival is high. In Figure 3 similar curves are displayed for the medically treated patients. Many of these patients had events, and the

need for revascularization continued during the follow-up period. Cardiac survival, myocardial infarction–free survival, and freedom from death, myocardial infarction or coronary bypass surgery in the PTCA group are displayed in Figure 4. PTCA in this figure refers to a third PTCA after discharge after the second PTCA. Although cardiac survival is high, continuing events do occur in these patients. Note that revascularization procedures after the second PTCA occurred largely within the first year, consistent with a second episode of restenosis. The population undergoing coronary bypass surgery for restenosis was small. At 5 years there were no late deaths (10 patients followed over 5 years), and 93% freedom from myocardial infarction or death in the population treated with coronary bypass surgery.

From the variables in Tables I to III, the correlates of cardiac death are displayed in Table VI. The patient's age and the presence of diabetes were the primary correlates of survival. Five-year survival was 99.4 ± 0.4%, age <50 years; 96 ± 1%, age 50 to 59 years; 95 ± 2%, age 60 to 69 years; and 83 ± 6%, age ≥70 years. Five-year survival was 97 ± 1 without and 86 ± 5% with diabetes. Perhaps surprisingly, patients also had

FIGURE 1. *Top,* probability of a second episode of restenosis in nondiabetic patients. The *abscissa* is the time from first percutaneous transluminal coronary angioplasty (PTCA) to catheterization-proved restenosis. The *curves* represent the diameter stenosis (DS) before repeat PTCA. *Bottom,* probability of a second episode of restenosis in diabetic patients. The *curves* are oriented as described.
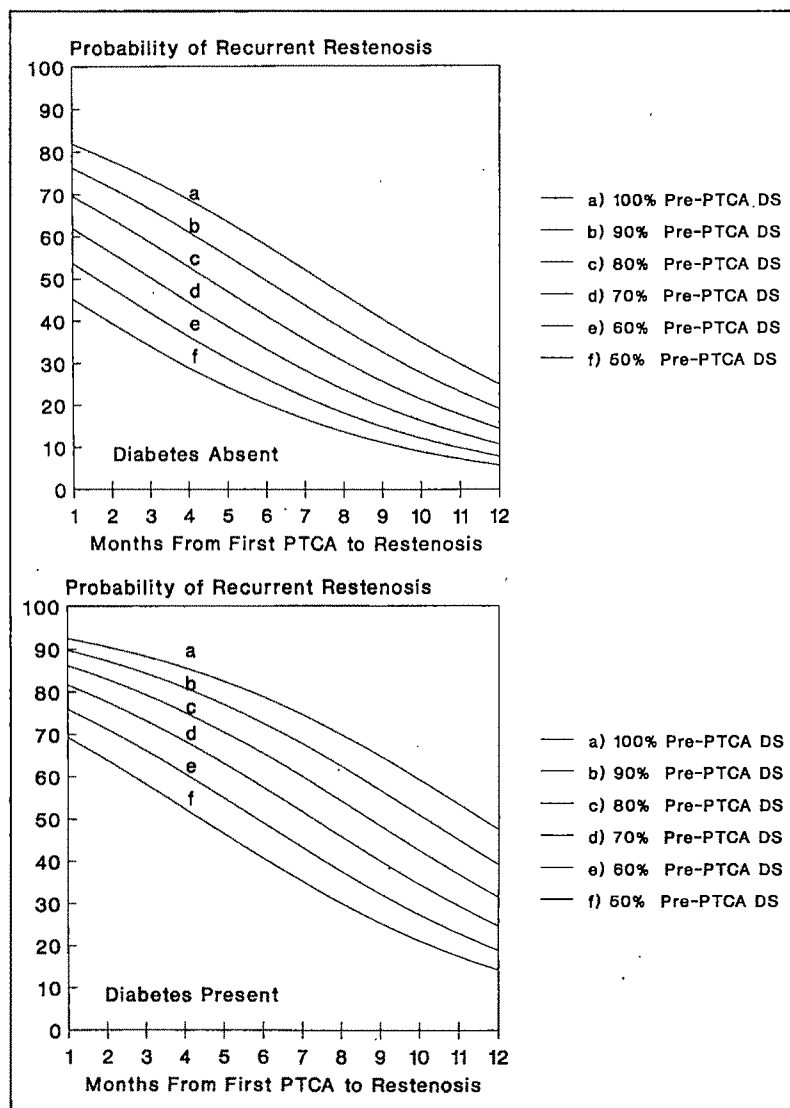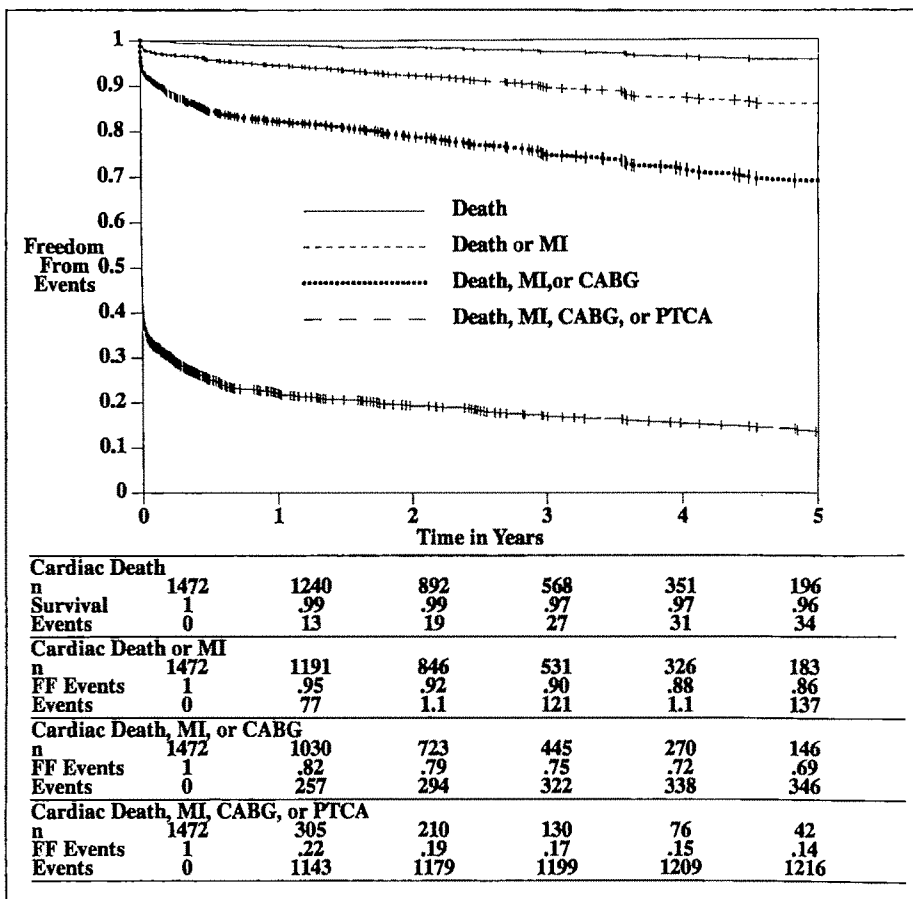
FIGURE 2. Five-year freedom from (FF) events in 1,472 patients who had elective percutaneous transluminal coronary angioplasty (PTCA) and restenosis at ≥1 site. The 4 curves represent cardiac survival, freedom from death or myocardial infarction (MI), freedom from death, MI or coronary artery bypass grafting (CABG), and freedom from death, MI, CABG or PTCA.

Figure 2 data

Legend: Death — Death or MI — Death, MI, or CABG — Death, MI, CABG, or PTCA

Cardiac Death						
n	1472	1240	892	568	351	196
Survival	1	.99	.99	.97	.97	.96
Events	0	13	19	27	31	34

Cardiac Death or MI						
n	1472	1191	846	531	326	183
FF Events	1	.95	.92	.90	.88	.86
Events	0	77	1.1	121	1.1	137

Cardiac Death, MI, or CABG						
n	1472	1030	723	445	270	146
FF Events	1	.82	.79	.75	.72	.69
Events	0	257	294	322	338	346

Cardiac Death, MI, CABG, or PTCA						
n	1472	305	210	130	76	42
FF Events	1	.22	.19	.17	.15	.14
Events	0	1143	1179	1199	1209	1216
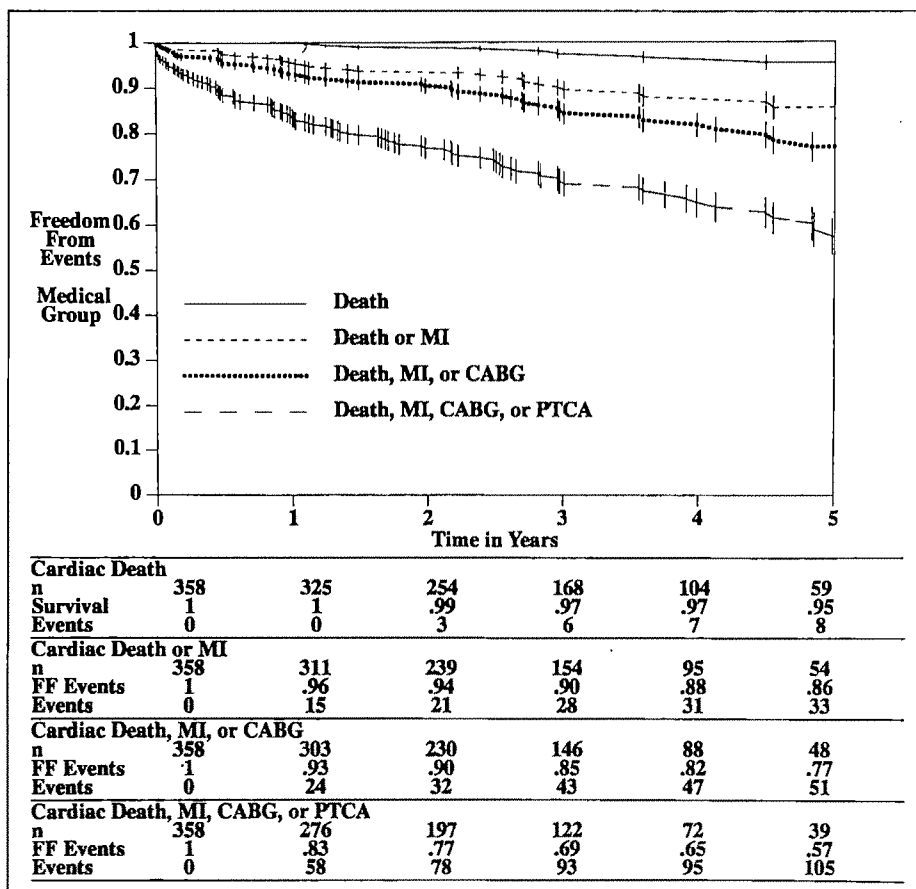
FIGURE 3. Five-year freedom from (FF) events in 358 patients who had elective percutaneous transluminal coronary angioplasty (PTCA) and restenosis at ≥1 site, and were treated medically initially when restenosis was diagnosed. The 4 *curves* represent cardiac survival, freedom from death or myocardial infarction (MI), freedom from death, MI or coronary artery bypass grafting (CABG), and freedom from death, MI, CABG or PTCA.

Figure 3 data (Medical Group)

Legend: Death — Death or MI — Death, MI, or CABG — Death, MI, CABG, or PTCA

Cardiac Death						
n	358	325	254	168	104	59
Survival	1	1	.99	.97	.97	.95
Events	0	0	3	6	7	8

Cardiac Death or MI						
n	358	311	239	154	95	54
FF Events	1	.96	.94	.90	.88	.86
Events	0	15	21	28	31	33

Cardiac Death, MI, or CABG						
n	358	303	230	146	88	48
FF Events	1	.93	.90	.85	.82	.77
Events	0	24	32	43	47	51

Cardiac Death, MI, CABG, or PTCA						
n	358	276	197	122	72	39
FF Events	1	.83	.77	.69	.65	.57
Events	0	58	78	93	95	105

slightly higher survival if the left anterior descending artery was dilated. The original number of vessels diseased, hypertension, and female gender were univariate correlates only. The ejection fraction did not correlate with survival, perhaps because most of the patients had normal or near-normal left ventricular function. The presence of angina at follow-up was also evaluated. At a mean follow-up of 35 ± 22 months, anginal status was available on 1,346 patients. Of 323 medically treated patients, 223 (69%) were angina free. Of 952 patients treated with repeat PTCA, 642 (67%) were angina free. Of 71 patients treated with coronary bypass surgery, 56 (79%) were angina free (difference not significant compared with PTCA or medically treated patients).

TABLE VI Correlates of Cardiac Death During Follow-Up

		Univariate Correlates			Multivariate Correlates		
	No. of Pts.	5-Year Survival	Chi-Square	p Value	Chi-Square	p Value	Coefficient
Age (years)			25	<0.0001	25	<0.001	0.084
<50	348	0.994 ± 0.004					
50–59	524	0.96 ± 0.01					
60–69	450	0.95 ± 0.02					
≥70	150	0.83 ± 0.06					
Diabetes mellitus			13	<0.0001	9.6	0.002	1.20
Absent	1,290	0.97 ± 0.01					
Present	182	0.86 ± 0.05					
Left anterior descending dilatation			4.9	0.025	5.9	0.015	−0.685
Not performed	549	0.92 ± 0.02					
Performed	923	0.97 ± 0.01					
Pre-PTCA vessels diseased			4.6	0.070	NS		
1 vessel	1,060	0.96 ± 0.01					
Multiple vessels	412	0.94 ± 0.02					
Hypertension			5.5	0.018	NS		
Absent	836	0.97 ± 0.01					
Present	636	0.94 ± 0.02					
Gender			5.2	0.014	NS		
Women	315	0.94 ± 0.02					
Men	1,157	0.96 ± 0.01					

Abbreviations as in Table I.

FIGURE 4. Five-year freedom from (FF) events in 1,039 patients who had elective percutaneous transluminal coronary angioplasty (PTCA) and restenosis at ≥1 site, and were treated by repeat PTCA when restenosis was diagnosed. The 4 *curves* represent cardiac survival, freedom from death or myocardial infarction (MI), freedom from death, MI or coronary artery bypass grafting (CABG), and freedom from death, MI, CABG or PTCA.

Cardiac Death						
n	1039	848	593	370	230	126
Survival	1	.99	.98	.97	.96	.95
Events	0	13	16	21	24	26
Cardiac Death or MI						
n	1039	816	565	349	215	118
FF events	1	.94	.92	.89	.87	.86
Events	0	58	76	88	96	99
Cardiac Death, MI, or CABG						
n	1039	727	493	299	182	98
FF events	1	.85	.80	.77	.73	.71
Events	0	158	187	204	216	220
Cardiac Death, MI, CABG, or PTCA						
n	1039	580	382	234	141	74
FF events	1	.67	.61	.57	.53	.51
Events	0	336	381	402	414	419
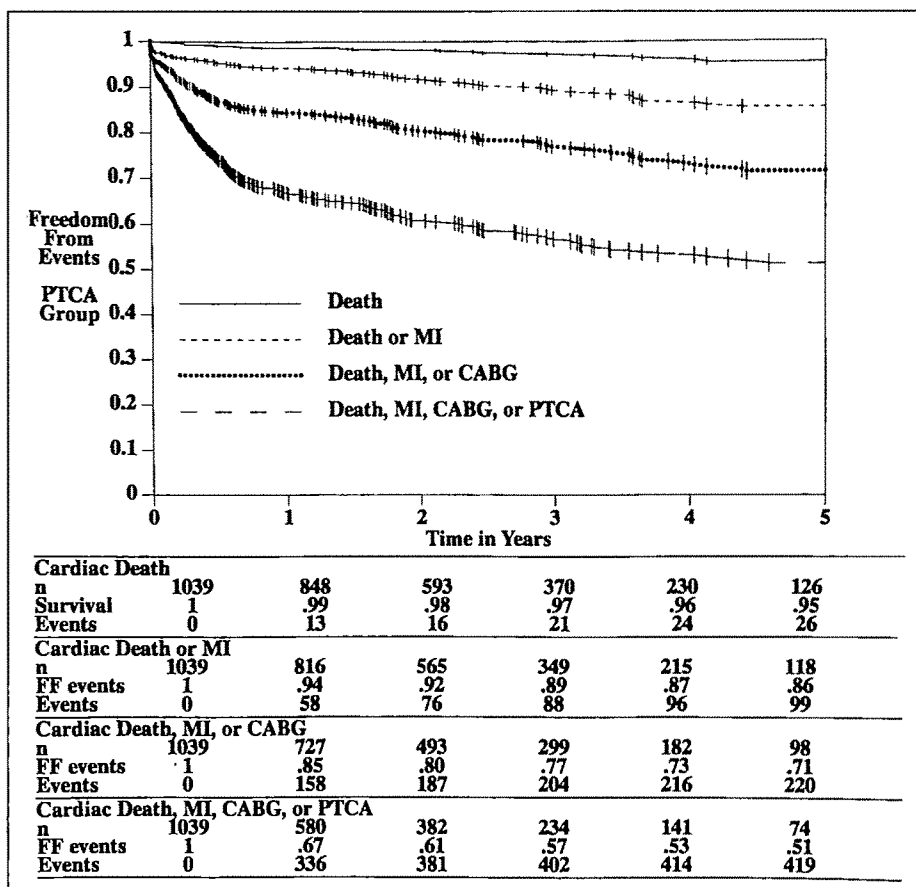
DISCUSSION

In this study the clinical outcome after angiographically documented restenosis is presented for a large population of patients. The majority were treated with repeat PTCA, with largely gratifying results. Whereas the ability to generalize the risks of a second episode of restenosis to other populations is somewhat limited by the restudy rate of 44%, the long-term results may be seen as somewhat reassuring as the 5-year survival was 0.95, and the myocardial infarction free survival was 0.86. However, additional procedures were frequently required. Older age and diabetes mellitus were the strongest correlates of late death. The other multivariate correlate, absence of a left anterior descending coronary artery dilatation, is surprising and without a clear explanation.

The results of repeat PTCA have been studied previously. The first report was by Williams et al[9] from the first National Heart, Lung, and Blood Institute PTCA registry. Of 1,880 patients in the registry with a successful initial procedure, repeat PTCA was performed in 203 for restenosis. There was a 1.5% myocardial infarction rate, 2% emergency coronary bypass surgery rate and no acute deaths. There was 0.8% mortality over several years, and 76% were event free. Angiographic follow-up was available in 62 patients with sustained success in 66%. Meier et al[8] reported on repeat PTCA in 95 of 514 patients who were initially treated successfully. The angiographic success rate was 95% with 8% complications. Repeat restenosis was noted in 26% of 92 patients with angiographic follow-up. Sugrue et al[10] reported on repeat PTCA for symptomatic restenosis in 74 of 694 original PTCAs. Success was achieved in 74% using a demanding ≥40% reduction in percent diameter narrowing. Acute occlusion occurred in 7%, and 12% required emergency coronary bypass surgery. At 113 weeks, 60% were asymptomatic. Recent reports have focused on a second restenosis. Black et al[11] studied 151 patients with angiographic follow-up out of an original population of 384 patients with 1-vessel disease and restenosis. The multivariate predictors of a second restenosis were an interval of <5 months to the first restenosis, male gender, lesion length of >15 mm, and >1 site dilated at the second PTCA. Quigley et al[12] studied 117 patients after repeat PTCA. Primary success was achieved in 98%, and there was 1 in hospital death. At follow up 218 ± 160 days later, 63% were angina free with no late death, 2.6% having a late myocardial infarction. Follow-up angiography was available in 100. Recurrent restenosis was noted in 32%. The correlates of recurrent restenosis were unstable angina, diabetes, hypertension and a short interval from the first to second PTCA. The current study adds to the previous studies by the much larger sample size, inclusion of patients with restenosis treated initially medically or with coronary bypass surgery, and by the long and complete follow-up. The correlates of recurrent restenosis were similar, with diabetes and a short period from first PTCA to first restenosis being relatively consistent correlates. That a short period from first dilatation to first restenosis predicts a second episode of restenosis may reflect a more aggressive process of myointimal proliferation.

In this study, we have confirmed that restenosis can be successfully managed with low morbidity and mortality and gratifying long-term results. The overall survival and myocardial infarction–free survival are similar to series of patients after PTCA that include patients with and without restenosis.[18-21] This is not entirely surprising because most of the patients had normal overall left ventricular function and 1-vessel disease. While restenosis remains a limitation of PTCA, these patients can be managed with excellent long-term results. The selection of the appropriate form of therapy cannot be determined from grouped data such as presented here. There is a tendency to treat female patients medically, perhaps because of fears of poorer outcome in women. Clearly, there is selection toward coronary bypass surgery in patients with multiple vessel disease and away from coronary bypass surgery in older patients. There is also a tendency to treat more mildly restenosis lesions medically. Whereas the excellent initial results of repeat PTCA may lead toward this form of therapy, recurrent restenosis is a concern. Thus, there are disturbingly frequent additional procedures beyond a first repeat dilatation. The therapy chosen should reflect a careful integration of the clinical and angiographic status of each patient, with consideration of the potential for further cardiovascular events and risks of a second episode of restenosis.

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Usefulness of a Postoperative Exercise Test for Predicting Cardiac Events After Coronary Artery Bypass Grafting

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The predictive value of a postoperative exercise test in terms of cardiac events after coronary artery bypass grafting (CABG) was prospectively studied in 231 consecutive patients. During a 5-year follow-up there were 28 cardiac events (12%), of which 15 were cardiac deaths (13 sudden), and 13 were nonfatal myocardial infarctions. There was no difference in the rate of graft patency between groups with and without cardiac events, but ejection fraction was lower in patients with than without events (51 ± 16% vs 58 ± 10%; p <0.05). Duration of the exercise test was shorter, and maximal work load was lower in patients with cardiac events (p <0.05 for both). The prevalence of ≥1 mm ST-segment depression was 22% (symptomatic in 25%, and silent in 75%) and did not differ between groups with and without cardiac events. After adjustment for prognostic variables using the proportional hazards method, diuretic treatment (p = 0.007) and a low postoperative ejection fraction (p = 0.04) remained significant for predicting the risk of cardiac events within 5 years of CABG, but exercise duration and work load did not have any significant predictive value. Thus, the predictive value of a postoperative exercise test is limited, and signs of impaired left ventricular function are of greater significance for the 5-year prognosis after CABG than are those of myocardial ischemia.

(Am J Cardiol 1992;70:56–59)

Although exercise testing provides valuable prognostic information regarding patients with coronary artery disease, the role of postoperative exercise testing and other noninvasive techniques in determining the prognosis after coronary artery bypass grafting (CABG) is not well-established.[1-4] Exercise testing has been primarily used to define functional capacity to make recommendations regarding physical activity in the early postoperative period, whereas coronary angiography is usually reserved for patients with recurrent angina.[1] This prospective, consecutive, angiographically controlled investigation determines the predictive value of an exercise test in terms of cardiac events after CABG.

METHODS

The population consisted of 231 consecutive patients (209 men and 22 women, mean age ±55 years) who underwent recatheterization and performed an exercise test 3 months after CABG. Patients gave informed consent for these examinations. Clinical characteristics of patients are summarized in Table I.

Catheterization examinations: All patients underwent left-sided cardiac catheterization and angiography before and 3 months after CABG. Selective coronary and graft angiograms, and biplane left ventriculograms were obtained by the Judkins technique, and interpreted as described previously.[5] The myocardium jeopardy score was used to quantify the myocardium at risk for ischemia after CABG. This score and the left ventricular contractility scoring system were also described previously.[6]

Exercise test: Patients performed symptom-limited bicycle exercise tests on the day before catheterization. Work load began at 30 W, and was increased in 1-minute steps by 15 W for men and by 10 W for women.[5] Duration of exercise, maximal work load in the bicycle exercise test, and the reasons for stopping the tests were noted. Ischemia was defined as ≥1 mm horizontal or downsloping ST-segment depression measured 80 ms after the J point of the electrocardiogram. Digitalis therapy was stopped 2 weeks before the exercise tests.

Follow-up: A questionnaire was mailed to all patients. If a complete answer was not received, patients, or their relatives or primary physician were contacted by telephone. A cardiac event was defined as cardiac death or myocardial infarction. In cases of death, a detailed analysis of the manner of death was obtained by reviewing patient records and autopsy data (if available), and questioning witnesses about events before

death. Deaths were classified as cardiac or noncardiac. Cardiac deaths were considered sudden if they occurred within 1 hour of the onset of symptoms. In cases of myocardial infarction, the original documents were analyzed. Myocardial infarction was defined as a new occurrence of Q waves on an electrocardiogram, with a positive MB-fraction of creatine kinase being needed in cases of non-Q-wave infarctions.

Statistics: The standard t or Mann-Whitney test was used (when appropriate) to compare continuous data between groups. Chi-square or Fischer's exact t test was used to compare proportions. The proportional hazards method of Cox was used to adjust for the covariates of survival.

RESULTS

There were 28 cardiac events (12%) during 5-year follow-up, of which 13 (46%) were nonfatal myocardial infarctions. Of the 15 cardiac deaths (56%), 13 (87%) were sudden, and 2 patients (13%) died as a consequence of myocardial infarction.

Postoperative clinical and angiographic data in patients with and without cardiac events during follow-up are presented in Table I. Patients with cardiac events more frequently used diuretics than did those without such events, and their cardiac size in chest x-ray was more often enlarged. Graft patency did not differ between groups. Cineangiographic left ventricular wall motion abnormalities occurred more frequently in patients with cardiac events and they had a lower left ventricular ejection fraction and higher left ventricular volumes.

Exercise data: The data from the exercise tests are presented in Table II. Duration of exercise was shorter, and maximal work load was lower in patients with cardiac events, but there were no differences in maximal heart rate or systolic blood pressure between groups. The reason for stopping the exercise test, and the occurrence of ≥1 mm ST-segment depression was not significantly different between groups. The occurrence of painless ST-segment depression was comparable in both groups (17% of all patients). The sensitivity of ≥1 mm ST-segment depression for detecting ≥1 ischemic myocardial segment (jeopardy score ≥1) was 23% and its specificity was 82% (overall predictive accuracy 55%). Figure 1 presents the life-table analysis of patients with and without ST-segment depression during 5-year follow-up.

After adjustment for prognostic variables using the proportional hazards method, a low postoperative ejection fraction remained significant for predicting the risk of cardiac events within 5 years of CABG. Exercise duration and work load did not have any predictive value (Table III).

DISCUSSION

There have been a number of evaluations of the prognosis for patients after CABG, using either clinical, angiographic,[1,7-12] exercise[1,6,13-15] or ambulatory electrocardiographic[3-4] variables measured either before or after CABG. In agreement with the present findings, other investigators reported that the outcome after

CABG is mainly determined by left ventricular function.[6,10-12,16] The only clinical variable that helped to predict future cardiac events in the present study was use of diuretics. This finding is in accordance with previous studies and may be related to history of heart failure rather than to use of diuretic drugs, per se.

Duration of the exercise test was shorter, and maximal work load was lower in patients with cardiac events, but these variables were not powerful enough to predict the outcome in a Cox regression model. The correlation of exercise duration with prognosis was variable in previous studies, probably due to differences in patient cohorts,[1,17] but our data suggest that reduced exercise tolerance may be partly related to impaired left ventricular function, and therefore its independent predictive power for future cardiac events is rather low.

Residual ischemia after CABG was not in itself an adverse prognostic sign, as evidenced by the jeopardy score, ST-segment depression and graft patency. In agreement with the present findings, Dupach et al[1] found that the predictive power of the abnormal exercise electrocardiographic response for predicting cardi-

TABLE I Comparison of Postoperative Clinical and Angiographic Data Between Patients With and Without Cardiac Events

	Patients Without Events (n = 203)	Patients With Events (n = 28)	p Value
Age (yr)	55 ± 7	53 ± 7	NS
Women/men	21/182	1/27	
Prior MI			
0	100 (49%)	13 (46%)	NS
1	78 (39%)	10 (36%)	NS
≥2	25 (12%)	5 (18%)	NS
NYHA class			
1–2	173 (85%)	21 (75%)	NS
3–4	30 (15%)	7 (25%)	NS
Medication			
Digitalis	109 (54%)	19 (68%)	NS
Diuretic	43 (21%)	14 (50%)	<0.05
β-blocking agent	170 (84%)	20 (71%)	NS
Calcium antagonist	36 (18%)	4 (14%)	NS
Total cholesterol (mmol/L)	7.2 ± 1.4	7.0 ± 1.5	NS
HDL cholestrol (mmol/L)	1.1 ± 0.3	0.9 ± 0.2	NS
Triglycerides (mmol/L)	2.2 ± 1.4	2.6 ± 2.1	NS
Chest x-ray			
Enlarged heart	86 (42%)	19 (68%)	<0.05
Congestion	34 (17%)	7 (25%)	NS
Angiographic data			
Graft patency 100%	106 (52%)	12 (43%)	NS
≥1 graft occluded	97 (48%)	16 (57%)	NS
Jeopardy score			
0	100 (49%)	12 (43%)	NS
1	81 (40%)	11 (39%)	NS
2	18 (9%)	4 (14%)	NS
3	4 (2%)	1 (4%)	NS
Contractility score			
≤11	182 (90%)	21 (75%)	NS
≥12	21 (10%)	7 (25%)	<0.05
Left ventriculogram			
LVEDVI (ml/m²)	78 ± 39	93 ± 34	<0.05
LVESVI (ml/m²)	34 ± 17	50 ± 34	<0.05
LVEF (%)	58 ± 10	51 ± 16	<0.05

HDL = high-density lipoprotein; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MI = myocardial infarction; NS = not significant; NYHA = New York Heart Association.

TABLE II Exercise Data Three Months After Coronary Artery Bypass Grafting in Patients With and Without Cardiac Events

	Patients Without Events (n = 203)	Patients With Events		
		Total (n = 28)	Death (n = 15)	Myocardial Infarct (n = 13)
Duration (min)	8.5 ± 3.4	7.2 ± 2.3*	7.2 ± 2.5	7.2 ± 2.0†
Work load (W)	108 ± 42	96 ± 26*	96 ± 28	96 ± 26
HR at rest (beats/min)	72 ± 13	75 ± 14	71 ± 12	79 ± 15
HR max (beats/min)	126 ± 26	124 ± 22	124 ± 20	124 ± 24
Systolic BP at rest (mm Hg)	135 ± 18	139 ± 19	142 ± 20	135 ± 17
Systolic BP max (mm Hg)	177 ± 32	171 ± 23	173 ± 19	168 ± 28
End point				
Angina	52 (26%)	8 (29%)	3 (20%)	5 (38%)
Dyspnea	43 (21%)	7 (25%)	5 (33%)	2 (15%)
Other	108 (53%)	13 (46%)	7 (47%)	6 (46%)
ST-segment ↓ ≥1 mm	42 (21%)	10 (36%)	5 (33%)	5 (38%)
Without angina	32 (16%)	7 (25%)	4 (27%)	3 (23%)
With angina	10 (5%)	3 (11%)	1 (7%)	2 (15%)

*$p < 0.05$ between patients with and without cardiac events; †$p < 0.05$ between patients with myocardial infarction and without cardiac events.
BP = blood pressure; HR = heart rate; max = maximal; ↓ = depression.

ac events was low during 2-year follow-up in patients studied because of recurrence of symptoms. Similarly, McConahay et al[13] reported that ST-segment depression during postoperative exercise testing was not associated with a higher risk of death or infarction. A recent report from the Coronary Artery Surgery Study[2] randomized population showed that survival 12 years after bypass surgery was better for patients without ischemia on exercise testing performed 6 months after CABG. Discrepancy in these studies may be due to differences in follow-up time, population and experimental design. In addition, methodology of the exercise test (bicycle vs treadmill) may have influenced the results.[18] In contrast to previous studies, the present survey was performed at 1 center with a uniform exercise protocol on a series of consecutive patients who had undergone CABG. Fur-

thermore, all patients underwent postoperative angiography that provided the possibility to relate exercise data to graft patency and left ventricular function. A potential limitation is that the study was performed 3 months after CABG, and therefore some early cardiac events were not included.

The sensitivity of ST-segment depression in detecting the amount of the myocardium still in jeopardy was low, which may be due to the poor ability of ST-segment changes to detect small ischemic areas, concurring with the results of McConahay et al.[13] Another study reported that almost 50% of a series of patients with exercise-induced ST depression after CABG had patent grafts.[19] Thus, it appears obvious that ST-segment depression has a fairly low predictive accuracy concerning graft patency and jeopardized myocardium after CABG. Although ST-segment depression was painless in 75% of our patients, the overall occurrence of asymptomatic myocardial ischemia was lower than that detected by ambulatory electrocardiographic examinations after CABG, in which it persisted in 20 to 30% of patients during follow-up of 1 to 12 months.[3-4] Egstrup[4] reported that CABG reduced the occurrence of painless ischemia, but its presence was still a powerful independent predictor of cardiac events during the following 9
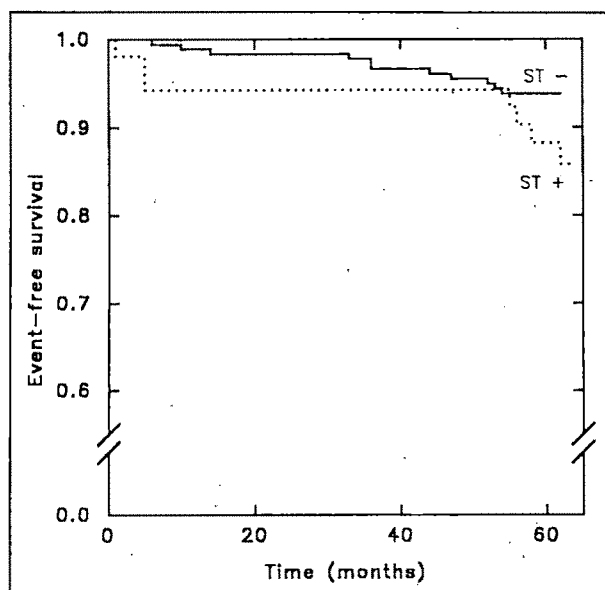
FIGURE 1. Kaplan-Meier life-table analysis of patients with and without ST-segment depression during 5-year follow-up.

TABLE III Cox Regression Analysis and Proportional Hazard Functions

Covariate	5-Year Coefficients	Standard Error of Coefficients	p Value
Clinical			
Diuretic usage	0.82	0.31	0.007
Cardiac size	0.55	0.31	0.07
Angiographic			
Postoperative EF	0.02	0.01	0.04
Exercise			
Duration (min)	0.07	0.07	0.3
Work load (W)	0.00	0.005	0.96

EF = ejection fraction.

months. However, Kennedy et al[3] found no association between asymptomatic ischemia and adverse clinical events, concurring with our results.

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Comparison of Patient-Reported Outcomes After Elective Coronary Artery Bypass Grafting in Patients Aged ≥ and <65 Years

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Older patients represent a growing proportion of patients undergoing coronary artery bypass grafting (CABG). Although functional benefits after CABG have been demonstrated, most assessments of outcomes have involved patients aged <65 years. Therefore, little is known concerning the impact of CABG on older patients compared with that on younger ones. A number of postsurgical (6 months) health-related quality-of-life outcomes (e.g., symptoms, cardiac functional class, instrumental activities of daily living, and emotional and social functioning) reported by patients aged <65 (n = 169) and ≥65 (n = 99) years who underwent elective CABG at 4 major teaching hospitals in Massachusetts and California were compared. The proportion of patients reporting cardiac-related symptoms after surgery did not vary by age, and quality-of-life outcome scores of younger and older patients did not differ even after adjustment for clinical and demographic characteristics. The exception to this was mental health status, an outcome for which older patients reported better functioning than did younger ones. On average, patients in the 2 age groups reported equivalent improvement over preadmission status in instrumental activities of daily living, and emotional and social functioning. The independent relation of clinical and sociodemographic factors to quality-of-life outcomes was also investigated. Patients who functioned better before admission, those with less severe co-morbid disease, and married patients reported better functioning after discharge. In general, older patients who underwent elective CABG reported functional benefits similar to those reported by younger ones, and the factors associated with better functioning did not vary by age group.

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The use of coronary artery bypass grafting (CABG) has increased steadily over the past 20 years, particularly for patients aged ≥65 years,[1] as well as for those who are in poor preoperative condition and have associated medical diseases.[2] As improvements in surgical technique and perioperative care have reduced the mortality associated with this procedure, the effects of CABG on functional status and quality of life have assumed increased importance in the decision to operate. Most studies of outcomes after CABG have focused on mortality or surgical complications,[2–6] and those that have focused on functional status typically have excluded older patients.[7] Because older patients account for a progressively larger proportion of those undergoing CABG, it is important to document whether the emotional and functional status benefits reported by younger patients are also experienced by older ones (i.e., whether reported benefits are equivalent across age groups). We compared a number of health-related quality-of-life outcomes (both condition specific and generic) reported by patients aged < and ≥65 years who underwent elective CABG at 4 major teaching hospitals in Massachusetts and California. We also examined the clinical and demographic predictors of positive quality-of-life outcomes, and investigated whether these predictors varied across age groups.

METHODS

Patient sample: From September 1985 to February 1987, we identified all patients aged >17 years who underwent CABG at 2 hospitals in Massachusetts (Brigham and Women's Hospital, and New England Medical Center) and at 2 hospitals in California (Stanford Medical Center, and University of California, San Francisco Medical Center). Because our intent was to study elective CABG, we excluded all patients admitted >3 days before surgery, transferred from another acute care hospital, admitted through an emergency room, or directly to a coronary or intensive care unit, or treated preoperatively with intravenous nitroglycerin. We also excluded patients who had CABG or acute myocardial infarction within the month before hospitalization. Therefore, selected patients were at relatively low risk for major adverse postoperative outcomes such as death and severe disability. Each hospital randomly selected up to 100 patients who met the study criteria. We excluded from analysis 3 patients who died during hospital stay, and 4 with a length of stay >30 days. Thus, our sample consisted of 344 patients.

Data: Data sources consisted of medical records and patient surveys. Data abstracted from the medical rec-

ord included the following: (1) patient characteristics, status regarding unstable angina at admission, history of acute myocardial infarction, American Society of Anesthesiologists' classification (I–IV), extent of coronary disease, presence or absence of diabetes needing treatment with insulin, co-morbid disease severity and symptomatic heart failure; (2) characteristics of the operation, number of days of intubation, and use of internal mammary artery graft; (3) reoperation status during index hospitalization; and (4) presence or absence of major postoperative complication (any 1 of the following: pneumonia, hypotension, coma, neuropathy, pulmonary embolism, septicemia/bacteremia, shock, myocardial infarction, congestive heart failure, stroke, renal failure or cardiac arrest).

Although left ventricular ejection fraction is an important predictor of functional status, it was recorded in the medical record for only 65% of patients and thus was not used as a case-mix indicator in our analyses.

The co-morbidity index used is an adaptation of the approach of Greenfield et al,[8] which documents from the medical record both the severity of co-morbid diseases and their impact on physical status. Conditions assessed included hypertension, cerebral vascular, respiratory and peripheral vascular diseases, diabetes mellitus, malignancies, liver disease, arthritis and gastrointestinal disease. Of these conditions, we used the most severe co-morbid disease and physical status assessment to classify each patient. Co-morbidity levels were defined as follows: I — no co-morbid condition; II — mild to moderate co-morbid condition, with no more than moderate physical impairment; III — severe co-morbid condition or physical impairment.

Health status questionnaire: Approximately 6 months after discharge, we mailed all eligible patients a health status survey containing questions concerning symptoms, and physical, social and emotional functioning. We selected a 6-month assessment period to minimize the variability in postdischarge outcomes due to the normal recovery process. Patients who did not return the original questionnaire were sent a second one. We attempted a telephone interview with those who did not respond to the second mailing.

Condition-specific outcome measures included questions about cardiac-related symptoms (e.g., dyspnea) that occurred during the month before survey completion, and an adaptation of the Specific Activities Scale developed by Goldman et al.[9] The Specific Activities Scale measures cardiac functional class on a scale of I (can perform activities needing ≥7 metabolic equivalents) to IV (cannot or does not perform activities needing ≥2 metabolic equivalents).

Generic measures of health status outcome consisted of a 6-item instrumental-activities-of-daily-living scale, a 3-item social activity scale and a 5-item mental health scale,[10] all adapted from the Functional Status Questionnaire.[11] For each generic health outcome measure, we ascertained preadmission status by asking patients (independent of postdischarge assessments) to complete the scales relative to functioning during the month before hospitalization. Scores for each of these measures

have been linearly transformed to a scale of 0 (least functional) to 100 (most functional) for ease of interpretation and presentation.

We also asked patients to indicate the number of times they had visited a physician since discharge, the number of postdischarge hospitalizations, and whether they had spent any time in bed because of illness during the month before assessment.

Statistical analyses: Our primary analyses focused on whether the level of functioning, and the correlates of health outcomes differed between patients aged < and ≥65 years. We compared mean outcomes scores, adjusting for demographic and clinical characteristics using analysis of covariance.[12] We adjusted for the following covariates: gender, race (white/nonwhite), education level, marital status, severity of co-morbid dis-

TABLE I Demographic, Clinical, Process-of-Care and Preadmission Characteristics by Age Group for Patients Responding to an Outcomes Questionnaire Six Months After Coronary Artery Bypass Grafting Surgery

	Value for Age Group*	
	< 65 Years†	≥ 65 Years‡
Demographic characteristics		
White race	149 (90.8)	90 (92.8)
Education		
< high school	42 (25.6)	26 (27.1)
High school graduate	34 (20.7)	21 (21.9)
Some college	49 (29.9)	23 (23.9)
College graduate	20 (17.2)	11 (11.5)
Married	135 (81.3)	83 (83.8)
Clinical characteristics		
Unstable angina	19 (11.2)	13 (13.1)
Diabetes treated with insulin	12 (7.1)	4 (4.0)
Acute myocardial infarction		
Never	81 (47.9)	45 (45.4)
> 3 months	60 (35.5)	39 (39.4)
< 3 months	28 (16.6)	15 (15.2)
Co-morbidity index		
I	46 (27.4)	17 (17.2)
II	117 (69.6)	74 (74.8)
III	5 (2.9)	8 (8.1)
American Society of Anesthesiologists' classification level IV	52 (31.1)	37 (38.1)
Symptomatic heart failure	14 (8.3)	14 (14.1)
Extent of coronary narrowing§		
1 vessel	6 (3.6)	2 (2.1)
2 vessels	48 (28.7)	19 (19.6)
3 vessels	93 (55.7)	51 (52.6)
Left main	20 (11.9)	25 (25.8)
Any major complication	57 (33.7)	43 (43.4)
Reoperation	7 (4.1)	6 (6.1)
Process-of-care characteristics		
Internal mammary artery graft present§	44 (73.9)	39 (60.6)
No. of days of intubation	1.0 ± 0.8	1.2 ± 1.6
No. of grafts	3.3 ± 0.9	3.3 ± 1.1
Preadmission functional status		
Intermediate activities of daily living	69.1 ± 22.9	68.3 ± 25.9
Mental health§	63.9 ± 19.9	70.7 ± 18.4
Social activities	84.8 ± 23.6	83.2 ± 27.1

*Values are presented either as the number (%) or as the mean ± standard deviation.
†Age range 37 to 64 years; ‡age range 65 to 79 years.
§p <0.05.

TABLE II Percentage of Patients Reporting Postoperative Cardiac-Related Symptoms

Symptom	Percentage in Age Group*	
	< 65 Years	≥ 65 Years
Exertional dyspnea	25.3	18.9
Ankle edema	20.0	18.6
Orthopnea	9.0	12.4
Awakening due to shortness of breath	7.2	7.3

*For each symptom, statistically significant differences did not occur.

TABLE III Postoperative Specific Activity Scale Scores by Age Group

Specific Activity Scale Score	Percentage in Age Group*	
	< 65 Years	≥ 65 Years
I	67.9	58.2
II	14.5	19.8
III	15.7	22.0
IV	1.9	0.0

*Distribution of Specific Activity Scale scores did not significantly differ across age groups.

TABLE IV Mean Postdischarge Outcome Scores by Age Group

Outcome	Unadjusted		Adjusted	
	< 65 Years	≥ 65 Years	< 65 Years	≥ 65 Years
Intermediate activities of daily living*	88.6	87.9	88.2	88.5
Social activities*	94.1	96.7	94.1	97.2
Mental health*	72.1	78.7‡	73.3	77.5‡
Specific activities scale†	1.5	1.6	1.6	1.6

*Covariates: preadmission health status, gender, race, education level, marital status, co-morbidity, reoperation and preadmission acute myocardial infarction status, number of days of intubation, presence or absence of unstable angina at admission, diabetes treated with insulin, internal mammary artery graft, major postoperative complication, preadmission symptomatic heart failure status and left main artery disease.
†Covariates: preadmission intermediate activities of daily living, gender, race, education level, marital, co-morbidity, American Society of Anesthesiologists' and preadmission acute myocardial infarction status, number of days of intubation, reoperation status, presence or absence of unstable angina at admission, diabetes treated with insulin, internal mammary artery graft, major postoperative complication, preadmission symptomatic heart failure status and left main artery disease.
‡p <0.05.

ease, American Society of Anesthesiologists' classification, reoperation status, number of days of intubation, preadmission functional status, unstable angina on admission, symptomatic heart failure, diabetes treated with insulin, prior acute myocardial infarction, left main disease, major postoperative complication and internal mammary artery graft. Finally, we used multiple linear regression analysis to identify which demographic and clinical characteristics were independent determinants of each quality-of-life outcome.

RESULTS

Sample description: More than three quarters (78%) of the 344 patients returned questionnaires. The 268 respondents were more likely to have left main artery stenosis than were nonrespondents, but there were no other significant clinical or demographic differences between the 2 groups.

Demographic and clinical characteristics for patients aged <65 (n = 169) and ≥65 (n = 99) years are listed in Table I. Most patients in each group were men, white and married, and had at least a high school education. Few patients (11 to 13%) had unstable angina at admission. Almost 50% of patients in each group had never had an acute myocardial infarction, and approximately 33% were admitted with an American Society of Anesthesiologists' level IV classification. Older patients were significantly more likely than were younger ones to be admitted with left main disease. The proportion of patients presenting with symptomatic heart failure did not vary by age group. Younger patients received an internal mammary artery graft more often than did older ones. Older patients also tended to have more severe comorbid disease, but this difference was not statistically significant. Among the preadmission health status measures, only mental health differed significantly between age groups; older patients reported better preadmission mental health than did younger ones.

Cardiac-related symptoms and resource use after surgery: Table II lists the proportions of younger and older patients who had each of 5 cardiac-related symptoms during the month before the postdischarge survey. The most frequently reported symptoms in each age group were exertional dyspnea and peripheral edema. The proportion of patients reporting each individual symptom did not vary by age group. Specific Activities Scale scores also did not vary as a function of age (Table III). Most patients in each age group reported that they were able to perform activities needing ≥7 metabolic equivalents (e.g., carry ≥24 pounds up a flight of steps).

Further evidence of high postoperative functioning level was the finding that less than one fifth of older (18.6%) and younger (13.5%) patients reported any time in bed as a result of health problems during the month before assessment.

Between discharge and assessment, older patients visited physicians as often as did younger ones (mean number of visits ± standard deviation: 5.5 ± 4.8 and 5.6 ± 6.3, respectively). Furthermore, patients in the 2 groups were hospitalized with similar frequency (27.3 and 21.3% for older and younger patients, respectively).

Age differences in health-related quality-of-life outcomes: The unadjusted and adjusted mean scores for each quality-of-life outcome are listed in Table IV. For both condition-specific and generic outcome measures, patients reported a high level of functioning. Patients in both age groups reported near perfect social functioning, and instrumental-activities-of-daily-living scores were also high. Only mental health scores differed between age groups, with older patients reporting better functioning than younger ones. These results remained the same when adjusted mean scores were compared.

Postsurgical change in health-related quality-of-life outcomes: Figure 1 displays the degree of change in instrumental-activities-of-daily-living score, mental health and social activity functioning reported by patients over the 6 month postdischarge period. For each health status indicator, younger and older patients reported comparable improvement in functioning. Pa-

tients reported the greatest improvement in instrumental-activities-of-daily-living score (approximately 20 points). This level of improvement is approximately equal to the difference between the average instrumental-activities-of-daily-living score reported by patients of Specific Activities Scale class III and that reported by those of class II. We obtained similar results when each of the change scores was adjusted for demographic and clinical factors used in the analyses described previously.

Predictors of health-related quality-of-life outcomes: Three variables emerged as consistent predictors of postdischarge functioning. For all measures, patients with less severe co-morbid disease functioned better 6 months after discharge than did those with more severe co-morbidity. Better functioning before surgery predicted better postoperative functioning for all generic health outcome measures. Finally, married patients reported better functioning than did unmarried ones on all scales, except the social activities scale.

Several other variables were significant predictors within specific regression models. Patients with insulin-dependent diabetes functioned more poorly on the instrumental-activities-of-daily-living and social activities scales than did other patients. White patients and women reported less cardiovascular disability 6 months after CABG than did their nonwhite and male counterparts.

Age was a statistically significant, independent predictor of postsurgical functioning only in the model predicting mental health. Older patients reported better mental health scores. To determine whether age differentially influenced the relation between mental health functioning and the other significant predictors in the model, we ran a regression model that included preadmission and marital status, and co-morbidity severity by age interaction terms. The only significant predictor to emerge in this model was the main-effect preadmission mental health status term. Patients who reported better preadmission mental health functioning also reported better postsurgical mental health functioning.

DISCUSSION

In 1987, 46% of all patients who underwent CABG were aged >64 years.[13] For this age group, this figure represents nearly a twofold increase over the percentage of patients who underwent the procedure in 1979.[1] Increased use of the procedure with older patients has prompted interest in the effect of age on outcomes associated with CABG. However, most of this work has dealt with short-term outcomes such as length of stay, in-hospital complications and mortality. Older patients appear to do as well as younger ones with respect to these outcomes.[4,6] Our study advances beyond short-term outcomes, addressing the impact of CABG on the quality of life of older patients.

The data suggest that for a wide spectrum of activities, older patients function just as well as do younger ones after elective CABG. Both the magnitude of postoperative health status scores and the degree of improvement over preadmission functioning were equivalent in the younger and older groups. Furthermore, older patients did not report poorer cardiac functional

class, more postoperative symptoms or more postsurgical hospitalizations and visits to physicians than did younger ones.

Our sample was not representative of all patients undergoing CABG in the United States, because only elective cases from 4 major teaching hospitals were included. However, given the high return rate for the questionnaire, and the similarity between questionnaire responders and nonresponders, this sample was probably representative of all patients undergoing elective CABG at these hospitals during the study period. A larger scale effort would be needed to determine whether the results reported here can be generalized to the broader population of CABG patients. Furthermore, because few patients aged >74 years underwent CABG at the hospitals in our study (5%), it will be important to document the quality-of-life benefits in this group, especially as the number of older patients who undergo the procedure increases.

Our inability to use left ventricular ejection fraction in our analyses owing to missing data was disappointing. The absence of documentation of this important variable in a substantial proportion of medical records reinforces the need for systematic collection of clinically relevant data, so that case mix can be controlled for to the best extent possible in studies of this type.

Our results generally confirm those of several other researchers[7,14-16] who assessed health-related quality-of-life outcomes in samples of younger patients after CABG. Each of these studies documented significant improvement after surgery, as reflected by a variety of disease-specific and generic health status outcomes. These studies reported improved functioning by as early as 3 months[15] and certainly by 6 months[14] after discharge. This time frame is consistent with our data, which were collected 6 months after discharge.

Folks et al[17] found, as we did, that older patients reported better emotional functioning 6 months after discharge than did younger ones. They speculated that younger patients may have greater expectations for a full recovery and thus may be more likely to report distress because these expectations are not met. Expectations regarding recovery may be lower in older patients who consequently may report greater emotional well-being, because they have survived a complicated and
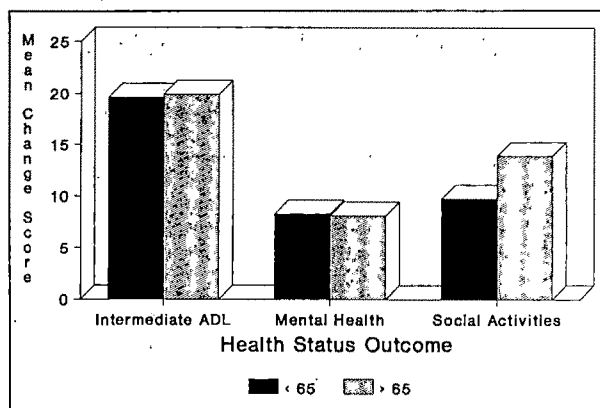
FIGURE 1. Unadjusted health status change scores by age group. ADL = activities of daily living.

potentially life-threatening surgical procedure with their functional capacities intact.

For most health status outcomes assessed, we found that better functioning after discharge correlated with better functioning before admission, less severe co-morbid disease at admission, and being married. It is not surprising that patients who function better on admission and are less sick do well after discharge. The advantage married patients appear to have with regard to health-related outcomes has been attributed to the social support available to them through their living situation.[18] However, this explanation has not been verified, and a better understanding of the process underlying this association may prove valuable.

Although elective CABG produced good functional outcomes among older patients in this study, we should emphasize the influence of patient selection in our investigation of the response of older patients to surgery. More older than younger patients presented with left main disease, but this was the only significant clinical difference between groups. Older and younger patients did not differ with respect to the presence of unstable angina on admission, diabetes needing insulin treatment, history of acute myocardial infarction, level of comorbidity, or American Society of Anesthesiologists' classification. Therefore, it is likely that physicians offer CABG to patients with similar clinical characteristics and that as long as patients meet these criteria, chronologic age is not a major factor in the decision to perform surgery or in the subsequent benefits of surgery.

One consequence of more frequent CABG for older patients is a greater demand on resources. We found that older patients selected for CABG benefit as much from this procedure as do younger patients. These results suggest that health planners and insurers should consider quality of life benefits as well as survival in resource allocation decisions.

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Increased Onset of Sudden Cardiac Death in the First Three Hours After Awakening

Stefan N. Willich, MD, MPH, Robert J. Goldberg, PhD, Malcolm Maclure, ScD, Lucy Perriello, MS, and James E. Muller, MD

A circadian variation of sudden cardiac death has been documented, but its relation to individual time of awakening and possible triggering events has not been studied in the general population. By monitoring of mortality records in 4 cities and towns in Massachusetts, 148 potential cases of sudden cardiac death were identified. In 94 cases, the informants listed on the death certificates were contacted, the diagnosis of sudden cardiac death was established, and a telephone interview was completed within a mean of 19 days (range 8 to 28) after the death.

The time of day of all 94 cases of sudden cardiac death (mean age 61 ± 9 years, 74% men) demonstrated a circadian variation (p <0.05) with a peak from 9:00 A.M. to 12:00 noon. An analysis of time of death adjusted for individual wake-times of the decedents demonstrated an increased onset of sudden cardiac death during the initial 3-hour interval after awakening with a relative risk of 2.6 (95% confidence interval 1.6, 4.2) compared with other times of the day.

The increased risk of sudden cardiac death soon after awakening suggests specific triggering factors or mechanisms that are particularly likely to occur during this time. The narrowing of the time interval during which the risk of sudden cardiac death is increased should facilitate the study of possible pathogenetic mechanisms and triggering factors of the disease and may aid in the design of more effective preventive strategies.

(Am J Cardiol 1992;70:65–68)

Sudden cardiac death is the leading cause of death in the United States and other industrialized countries, accounting for approximately 15 to 20% of all deaths.[1,2] The pathophysiologic mechanisms and possible triggers of this catastrophic event are poorly understood and a potential means of prevention are, therefore, inadequately developed. A new approach to investigation of the triggering mechanisms of sudden cardiac death is suggested by the documentation of a circadian variation in its occurrence with a significant morning peak.[3,4] A similar circadian pattern exists in the occurrence of nonfatal myocardial infarction,[5,6] an event closely related to sudden cardiac death.[7,8] The circadian pattern of myocardial infarction has now been documented to result primarily not from the absolute time of day but from an increased risk during the initial several hours after awakening.[9-11] The objective of the present study was to examine the relation between the time of sudden cardiac death and individual time of awakening.

METHODS

Data collection: Beginning in August 1989, death certificates were reviewed in 4 cities and towns in Massachusetts to identify potential cases of sudden cardiac death (with the cooperation of the city and town clerks in Worcester, Lowell and Framingham, and the Division of Vital Statistics at the Boston Department of Health and Hospitals). Because sudden cardiac death is not a diagnosis used routinely on death certificates, deaths reported with any of the following immediate or underlying causes were selected for possible inclusion in the study: sudden cardiac death, atherosclerotic cardiovascular disease, acute myocardial infarction, coronary artery disease, cardiac arrest or arrhythmia, ventricular fibrillation, occlusive coronary thrombosis, and electromechanical dissociation. Subjects were not included in the study if cancer, stroke or trauma was recorded as an underlying or contributing cause of death. Deaths that occurred in hospitalized or bedridden patients or in nursing home residents were not included since the endogenous and exogenous circadian rhythms are likely to be altered in these settings. The age range of the patients selected was limited to 30 to 80 years; younger patients may have an unusual cause of sudden cardiac death, while older persons often live alone or have older less reliable informants.

The names of the informants listed on the death certificate were retrieved and their telephone numbers obtained. Efforts were made to contact the informants within 30 days after the date of death. After consent to participate in the study was obtained, a standardized telephone interview was carried out with the spouse or

other persons who were able to describe the circumstances of death. Specific information about the decedents was obtained including coronary risk factors, concommitant disease, usual wake-time, and most recent time of awakening before death.

The following operational definition was used in identifying definite cases of sudden cardiac death: the subject, having been apparently well (in usual state of health), was observed to have died within 1 hour from the onset of symptoms, and the death could not reasonably be attributed (on the basis of information from the informant and death certificate) to some disease other than coronary artery disease. The inclusion of only cases of definite sudden cardiac death might introduce a selection bias since the likelihood of confirmation of the diagnosis is not randomly distributed over the course of a day. Therefore, also possible cases of sudden cardiac death were included, as identified by the following definition: the subject may have died within 1 hour from the onset of acute symptoms, and there was no apparent noncardiac cause of death on the basis of the information obtained from the informant and death certificate.

Data analysis: The time of sudden cardiac death was defined as time of onset of acute clinical symptoms before death. If the exact time of death was not known, the probability of death was evenly distributed during the interval during which the patient was known to have died. For example, the deaths of all patients who were known to be alive at 8:00 A.M. and dead at 4:00 P.M. were evenly distributed over the interval from 8:00 A.M. to 4:00 P.M. When the only information available concerning those persons who had died during sleep was that the patient was found dead in bed, the probability of death was evenly distributed between midnight and 6:00 A.M. or, for the wake-time adjusted analysis, during the 6 hours before wake-time. If time of death could not be estimated, the probability of death was evenly distributed over 24 hours.

The distribution of time of onset of sudden cardiac death as well as the relation to time after awakening was first tested for differences among light 3-hour intervals of the day with a chi-square test for goodness of fit. The risk of sudden cardiac death was expressed as an estimate of the relative risk with accompanying 95% confidence intervals during the 3-hour peak (index interval) of the circadian pattern compared with other times of the day (reference). The p values were 2-sided and were considered significant at <0.05.

RESULTS

A total of 148 death certificates were selected using the initial screening criteria. For 47 of the certificates reviewed the informant did not have a telephone, had an unpublished number, or could not be reached. In the remaining 101 cases, informants were contacted by telephone with an average delay of 19 days (range 8 to 28) after the day of death. In 94 cases (64% of total) the contacted informant consented to participate in the study, the diagnosis of definite or possible sudden cardiac death was confirmed, and the telephone interview was completed. The mean age of the sudden cardiac death cases was 61 ± 9 years and 74% were men. For 60% of the cases, the informant was the spouse, and for the remaining cases the informant was another relative or friend.

The time of occurrence of all 94 definite (n = 72) or possible (n = 22) cases of sudden cardiac death demonstrated a circadian variation (p <0.05) with an increased incidence during the late morning (Figure 1). The relative risk of onset of sudden cardiac death occurring from 9:00 A.M. to 12:00 noon was 1.7 (95% confidence interval 1.0, 2.8) compared with other times of day.

In 84 cases of sudden cardiac death, the most recent time of awakening before death (n = 52) or the usual wake-time (n = 32) was reported by the informants. Analysis of time of death adjusted for individual time of awakening demonstrated an increased risk of sudden cardiac death during the 3 hours after awakening (Figure 2). The relative risk of sudden cardiac death during the initial 3-hour interval after awakening was 2.6 (95%
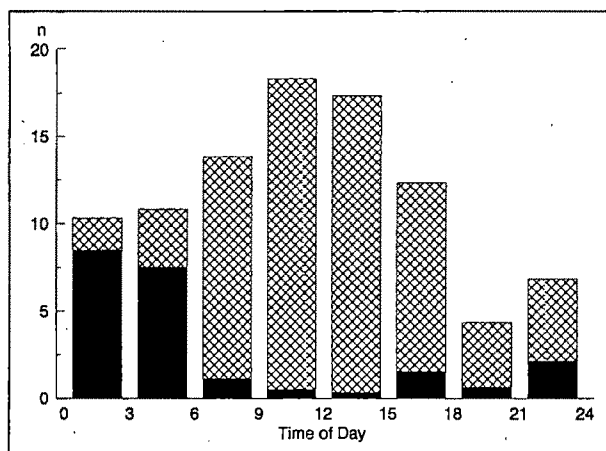
FIGURE 1. Time of death of all 94 definite (n = 72, *hatched areas*) or possible (n = 22, *dark areas*) sudden cardiac deaths showing a circadian variation with an increased incidence during the late morning compared with other times of day.
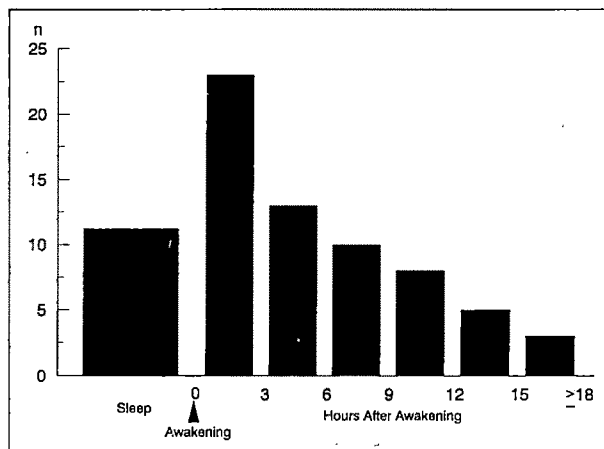
FIGURE 2. Time of sudden cardiac death adjusted for individual wake-times (n = 84) showing a significantly increased relative risk of 2.6 (95% confidence interval 1.6, 4.2) during the initial 3 hours after awakening compared with other times of day.

confidence interval 1.6, 4.2) compared with other times of the day. If only the usual time of awakening was used for the wake-time adjusted analysis, the findings were not significantly different.

DISCUSSION

The present study is to our knowledge the first to document that the morning increase of sudden cardiac death in the community is due to an increased relative risk in the first several hours after awakening. This relation is similar to that recently documented for nonfatal acute myocardial infarction[9-11] and transient myocardial ischemia.[12] Our findings are supported by the recent unpublished observation of Peters et al that sudden death of patients enrolled in the Cardiac Arrhythmia Suppression Trial began most frequently within 2 hours after awakening.

The increased risk of sudden cardiac death soon after awakening suggests specific triggering factors or pathophysiologic mechanisms, or both, that are particularly likely to occur during this time.[13] The observation that many cases of sudden cardiac death occur during other times of day is compatible with the hypothesis that triggering events occur at a lower frequency throughout the day. Although regular exercise is known to provide chronic protection against cardiovascular disease, strenuous physical exertion increases the acute risk of sudden cardiac death while it is being performed.[14,15] Less is known about the relative risk for moderate physical exertion and the duration of increased risk after a period of strenuous exertion. Anecdotal evidence suggests that other factors, such as sexual activity, unusual emotional stress, excess alcohol consumption or withdrawal from alcohol, may trigger sudden cardiac death and other cardiovascular diseases.[16-18] However, these observations have not yet been supported by systematic epidemiologic investigation.

The present study has several limitations, the greatest of which is the relatively small number of subjects studied. However, the identification of a statistically significant increase of sudden cardiac death soon after awakening with such a small number of cases suggests the importance of the phenomenon. The inability to contact approximately one-third of the informants may have introduced a selection bias, but the reasons for failure to contact them were probably unrelated to circumstances of the death. In some of the cases with unknown time of awakening on the day of death, the wake-time adjustment was based on the usual wake-time of the decedents. Although it appears unlikely, the possibility cannot be excluded that time of awakening was different on the day of death. Finally, the reliability and validity of the information provided by the informant (in most cases the spouse) is unknown.[19] Further studies therefore need to obtain more detailed information of the circumstances of sudden cardiac death, assess the range of valid data that can be provided by informants, and use a controlled study design for identification of triggering activities.[20]

Recent findings suggest that therapy with aspirin or β blockers (the agents consistently shown to reduce the risk of sudden cardiac death and myocardial infarction[21-23]) decreases the morning peak of acute coronary artery disease.[5,6,11,24] An immediate practical issue raised by the present finding is provision of optimal pharmacologic protection during the morning hours for patients already taking cardiac medication. This can be achieved with an aspirin preparation taken at any time of the day because the effect on platelets lasts considerably longer than 24 hours. However, a short-acting β-blocker taken at night may no longer have an adequate effect on the following morning. For this reason preference could be given to longer acting agents, although no trials have been conducted to compare the relative efficacy of short- versus long-acting agents in preventing sudden cardiac death.

Further research to determine the cause of the increase in sudden cardiac death after awakening could lead to a better understanding of the disease. In some cases, avoidable triggers may be identified, such as cigarette smoking or extreme physical exertion without training. In most instances, however, triggering may perhaps be caused by an activity that is either impossible or undesirable to avoid, such as assumption of upright posture or routine physical exertion. The preventive approach would then be to attempt to sever, through pharmacologic or behavioral means, the linkage between the activity and the risk of sudden cardiac death.

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Effectiveness of Loading Oral Flecainide for Converting Recent-Onset Atrial Fibrillation to Sinus Rhythm in Patients Without Organic Heart Disease or With Only Systemic Hypertension

Alessandro Capucci, MD, Tiziano Lenzi, MD, Giuseppe Boriani, MD, Giuseppe Trisolino, MD, Nicola Binetti, MD, Mario Cavazza, MD, Giovanni Fontana, MD, and Bruno Magnani, MD

Sixty-two patients with recent-onset (≤ 1 week) atrial fibrillation (New York Heart Association functional class 1 and 2) were randomized in a single-blind study to 1 of the following treatment groups: (1) flecainide (300 mg) as a single oral loading dose; or (2) amiodarone (5 mg/kg) as an intravenous bolus, followed by 1.8 g/day; or (3) placebo for the first 8 hours. Twenty-four-hour Holter recording was performed, and conversion to sinus rhythm at 3, 8, 12 and 24 hours was considered as the criterion of efficacy. Conversion to sinus rhythm was achieved within 8 hours (placebo-controlled period) in 20 of 22 patients (91%) treated with flecainide, 7 of 19 (37%) treated with amiodarone ($p < 0.001$ vs flecainide), and 10 of 21 (48%) treated with placebo ($p < 0.01$ vs flecainide). Resumption of sinus rhythm within 24 hours occurred in 21 of 22 patients (95%) with flecainide and in 17 of 19 (89%) with amiodarone (p = not significant). Mean conversion times were shorter for flecainide (190 $\pm$ 147 minutes) than for amiodarone (705 $\pm$ 418; $p < 0.001$). No major side effects occurred. At Holter monitoring, a pause of 9.3 seconds was observed in 1 asymptomatic patient treated with flecainide. Phases of atrial flutter with a ventricular rate ≤ 150 beats/min were detected before sinus conversion in 1 patient receiving placebo and in 2 receiving flecainide. In conclusion, flecainide administered orally in a single loading dose is highly effective in converting recent-onset atrial fibrillation to sinus rhythm and is more rapid than is intravenous amiodarone. This in-hospital regimen in patients without major organic heart diseases was safe and well-tolerated.

(Am J Cardiol 1992;70:69–72)

Atrial fibrillation (AF) is a common arrhythmia whose onset may induce disabling symptoms even in the absence of any organic heart disease[1,2] and often needs hospitalization to be converted to sinus rhythm. Pharmacologic treatment with digitalis glycosides (a milestone of the past) has lost much importance after publication of controlled studies.[3,4] Furthermore the standard treatment with quinidine needs a time-consuming titration.[5] The ideal medical therapy should be highly and rapidly effective, and easily administered, as well as safe, possibly reducing the time for hospitalization or even abolishing it. With this concept in mind, we compared (in a placebo-controlled single blind study) oral flecainide in a single loading dose with intravenous amiodarone, both of which are, theoretically, short-term regimens for acute conversion of AF to sinus rhythm. In this study, the effectiveness and safety of a single loading oral dose of flecainide were examined. Furthermore, because spontaneous reversion to sinus rhythm may occur in the first few hours,[3] a control group treated with placebo was introduced.

METHODS

Patients: During a 24-month period (March 1989 to March 1991), all patients with recent-onset AF admitted to our institutions were considered for this study. Recent-onset AF was defined as an arrhythmia of ≤ 7 days' duration. The main criteria to define the time of onset of the arrhythmia included either electrocardiographic documentation during hospitalization or an abrupt, well-defined onset of palpitations, with subsequent electrocardiographic evidence of AF on admission to the hospital.

Patients were excluded from the study if they met any of the following criteria: age >75 years, New York Heart Association functional class >2 or symptoms of heart failure on physical examination, mean ventricular rate (calculated over 15 RR cycles) during AF of <70 beats/min, previous myocardial infarction or angina pectoris, valvular heart disease or cardiomyopathy, electrocardiographic evidence of ventricular preexcitation or complete bundle branch block, previous electrocardiographic evidence of second- to third-degree atrioventricular or bifascicular block, known sick sinus syndrome, hypokalemia (K <3.5 mEq/liter), renal or hepatic insufficiency, severe hypoxia (oxygen partial pressure <55 mm Hg) or metabolic disturbances, or known thyroid dysfunctions. Patients were also excluded if they were currently receiving digitalis or antiarrhythmic

TABLE I Patients			
	Flecainide	Amiodarone	Placebo
No. of pts.	22	19	21
Men/women	14/8	10/9	11/10
Age (yr)	58 ± 12	59 ± 10	57 ± 11
Etiology (n)			
Without organic heart disease	15	12	16
Systemic hypertension	7	7	5
NYHA class I	20 (91%)	18 (95%)	19 (90%)
NYHA class II	2 (9%)	1 (5%)	2 (10%)
Previous AF episodes	1.5 ± 1.4	1.4 ± 1.3	1.6 ± 1.4
AF duration (hr)	28.0 ± 29.4	29.8 ± 30.2	27.0 ± 26.8
Atrial diameter by echocardiography (mm)	45 ± 5	46 ± 6	46 ± 8
Left atrial diameter >45 mm (n)	3	2	3

AF = atrial fibrillation; NYHA = New York Heart Association.

agents, or had taken 1 of these drugs ≤8 hours before entry in the study. All patients gave informed consent.

Study protocol: Complete medical hystory, physical examination, routine biochemical laboratory testing and a 12-lead electrocardiogram were obtained at baseline evaluation. Patients who fulfilled the eligibility criteria underwent 24-hour Holter monitoring. Patients were

subsequently observed for 60 minutes to check the stability of AF and, after electrocardiographic confirmation of arrhythmia persistence, were randomly allocated to 1 of the following treatment groups: (1) intravenous amiodarone (5 mg/kg in 20 ml of saline solution infused during 5 minutes, followed by 1.8 g in 500 ml of saline solution administered intravenously for 24 hours), plus 3 tablets of placebo as a single oral dose; (2) oral flecainide (3 tablets of 100 mg as single oral dose), plus 500 ml of saline solution intravenously administered for 24 hours; or (3) oral placebo (3 tablets as single oral dose), plus 500 ml of saline solution intravenously administered for 24 hours. The patients were not aware of the drug treatment they received; drug administration was in simple-blind fashion.

After drug administration, rhythm was continously monitored by telemetry, cuff blood pressure was measured every 2 hours, and a 12-lead electrocardiogram was recorded every hour in the first 4 hours and then every 2 hours until the end of the study.

Eight hours after randomization (placebo-controlled period), patients treated with placebo stopped the study and, in case of persistence of AF, underwent other pharmacologic treatments. For patients treated with amiodarone or flecainide, the observation period continued for the 24 hours. In each case, a 12-lead electrocardiogram was recorded when conversion to sinus rhythm occurred.

Holter monitor tapes were analyzed by a visual and computerized scanning system (Marquette 8000). Heart rate was analyzed in 15-minute samples for minimal, maximal and mean values, and rhythm analysis was confirmed in printouts of rhythm strips, including the periods immediately before and after conversion to sinus rhythm, to allow the assessment of RR intervals at conversion. Furthermore, phases of atrial flutter, (defined as regularization of atrial waves with regular RR intervals) and sudden RR interval prolongation >2 seconds were recorded.

After conversion to sinus rhythm, a cross-sectional echocardiogram was obtained in each patient, and left atrial diameter was measured in the left parasternal long-axis view.

Data analysis: The rate of conversion to sinus rhythm was assessed at 3, 8, 12 and 24 hours. Statistical analysis was performed using the chi-square test for comparison of the number of patients who had conversion to sinus rhythm. The paired t test was used for analysis of the electrocardiographic changes within each group, and analysis of variance and unpaired t test were used for comparison of mean conversion times between groups. A p value <0.05 was considered statistically significant.

RESULTS

Patients: Sixty-two patients were randomized to 1 of 3 treatments groups (19 to amiodarone, 22 to flecainide, and 21 to placebo). The 3 groups were comparable in terms of age, gender, etiology and New York Heart Association functional class (Table I). Furthermore, the number of subjects without any organic heart disease or with hypertension was similar. The duration of AF be-
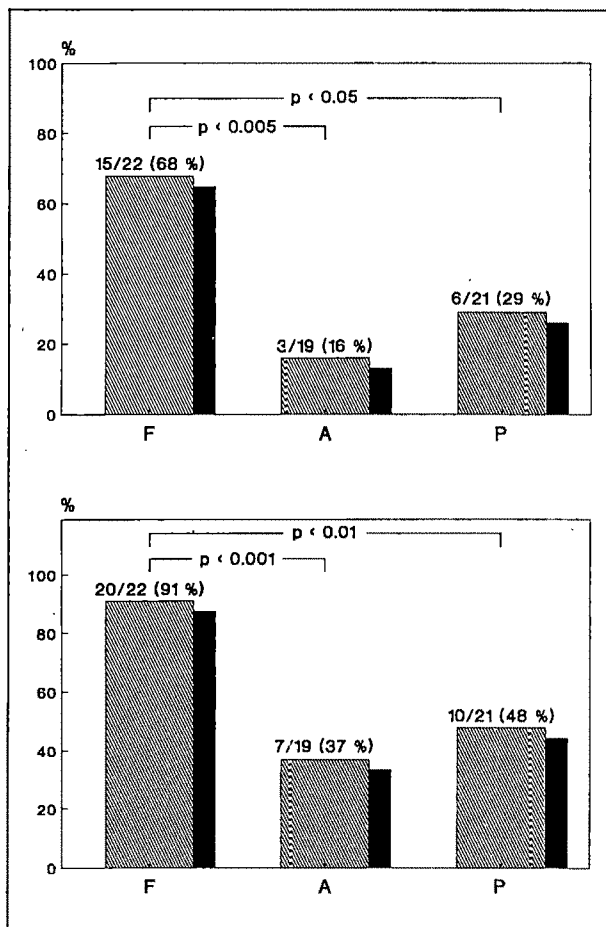
FIGURE 1. Conversion rates during placebo-controlled period at 3 *(top)* and 8 *(bottom)* hours. A = amiodarone; F = flecainide; P = placebo.

fore randomization varied from 1.3 to 121 hours, without differences in the mean values among the 3 groups (Table I). Only 10 to 14% of patients in each group had a dilated left atrium on echocardiographic evaluation (Table I).

Conversion of atrial fibrillation to sinus rhythm: The conversion rates during the placebo-controlled period (at 3 and 8 hours) are reported in Figure 1. Flecainide achieved a success rate of 68% at 3 hours and of 91% at 8 hours, and was significantly more effective than either amiodarone (16% at 3 hours [p <0.005], and 37% at 8 hours [p <0.001]) or placebo (29% at 3 hours [p <0.05], and 48% at 8 hours [p <0.01]). No statistical differences were found between amiodarone and placebo conversion rates.

Mean conversion times to sinus rhythm in the first 8 hours were 217 ± 136 minutes for amiodarone, 234 ± 139 for placebo, and 169 ± 90 for flecainide (p = not significant [NS]). Conversion to sinus rhythm occurred within 2 and 3 hours after drug administration in 68% (15 of 22) of patients treated with flecainide, 16% (3 of 19) treated with amiodarone, and 24% (5 of 21) treated with placebo.

Conversion to sinus rhythm was observed within 12 hours in 20 of 22 patients (91%) with flecainide and in 9 of 19 (47%) with amiodarone (p <0.01), and within 24 hours in 21 of 22 (95%) with flecainide and in 17 of 19 (89%) with amiodarone (p = NS). Mean conversion times to sinus rhythm within 24 hours were 190 ± 147 minutes for flecainide (range 120 to 780) and 705 ± 418 for amiodarone (range 60 to 1,200) (p <0.001).

Holter monitoring evaluation: Holter recordings were technically satisfactory and suitable for analysis in 15 patients treated with amiodarone, in 16 treated with flecainide and in 14 treated with placebo. Pauses ≥ 2 seconds were observed on conversion to sinus rhythm in 2 patients (2 seconds each) treated with amiodarone, in 2 (2.1 and 9.3 seconds, respectively) treated with flecainide and in 1 (3.1 seconds) treated with placebo. Mean RR intervals at AF interruption were 1.2 ± 0.3 seconds for amiodarone (range 0.8 to 1.8), 1.9 ± 2.3 for flecainide (range 0.8 to 9.3; p = NS) and 1.2 ± 0.5 for placebo (range 0.6 to 3.1; p = NS). Phases of atrial flutter were detected before conversion in 1 patient receiving placebo and in 2 receiving flecainide (ventricular heart rate 125 to 150 beats/min). Mean and maximal heart rates detected on Holter monitoring at basal conditions, and 1 hour before and immediately before sinus conversion are shown in Figure 2. Statistically, there were no significant differences in mean or maximal heart rate before conversion to sinus rhythm among the 3 groups.

Electrocardiographic interval changes: QRS intervals measured immediately after conversion to sinus rhythm were unchanged in comparison with basal values for either amiodarone (79 $\pm$ 8 vs 76 $\pm$ 6 ms; p = NS) or placebo (82 $\pm$ 11 vs 81 $\pm$ 10 ms; p = NS), whereas a mean increase of 30% occurred for flecainide (103 $\pm$ 17 vs 79 $\pm$ 10 ms; p <0.001). QRS values for flecainide were significantly prolonged compared with those for amiodarone and placebo (p <0.005). QTc intervals measured immediately after resumption of sinus rhythm did not differ significantly among the 3 groups

(399 $\pm$ 53 ms for amiodarone, 391 $\pm$ 40 for flecainide, and 394 $\pm$ 46 for placebo).

Adverse effects: No major side effects needing interruption of the study occurred. In 2 patients receiving amiodarone, superficial phlebitis was observed. Mild light-headedness was observed with flecainide in 1 patient.

DISCUSSION

Class 1C drugs (especially after intravenous administration) have been demonstrated to possess pharmacologic and electrophysiologic properties to facilitate conversion of AF to sinus rhythm.[7-17] Several studies documented a success rate between 67 and 95% with flecainide,[7-13] and between 43 and 81% with propafenone.[12,14-17] Intravenous amiodarone is also a generally adopted in-hospital treatment with a reported success rate between 25 and 81%.[17-21] The different success rates found in various studies can be mainly attributed to differences in average duration of AF, left atrial size, presence or absence of organic heart disease,[22,23] and absence of controls with placebo. In some studies, "recent onset" is defined as an episode of AF lasting ≤ 24 hours,[7,13] and "chronic" is defined as AF lasting >24 hours, whereas in other studies, AF lasting <15 days was considered as recent-onset arrhythmia.[16] Therefore the concept of recent and chronic AF was also a source of bias in previous studies.
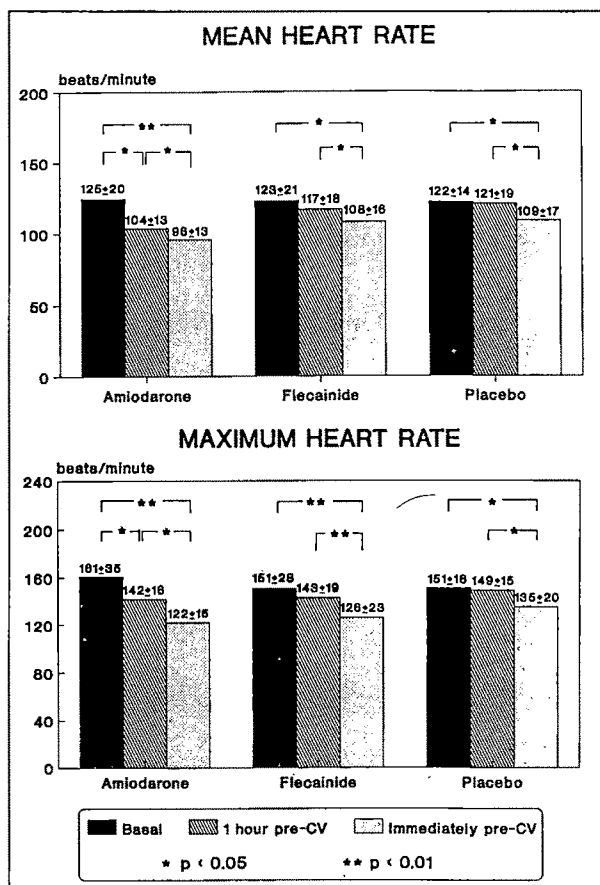
FIGURE 2. Mean and maximal heart rates during Holter recording at basal conditions, 1 hour before conversion (CV) to sinus rhythm, and immediately after conversion.

We did not find any controlled study of amiodarone in the setting of patients with recent-onset AF. Villani et al[7] performed a controlled study of oral flecainide and placebo in 37 patients, with success rates of 95 and 28%, respectively. The main result of our controlled study was the high percentage of short-term conversion to sinus rhythm in patients treated with an oral loading dose of flecainide (91% at 8 hours). Furthermore, mean conversion time was short (169 ± 90 minutes), and most positive responses occurred between the second and third hour of oral administration (i.e., during peak plasmatic level).[24] Analysis of the electrocardiographic changes with flecainide confirmed a widening of the QRS interval immediately after conversion; this parameter was previously shown to correlate with drug plasma levels.[25]

Comparison with a placebo group allowed us to observe that (at least until the eighth hour) amiodarone administered intravenously at the dosage used in this study (i.e., the generally adopted dosage)[17-19,21] was not superior to placebo in converting AF to sinus rhythm. Furthermore, 48% of patients with AF lasting <7 days spontaneously reverted to sinus rhythm a few hours after hospitalization.

The data at 24 hours showing a recovery of the efficacy rate in the amiodarone group are probably, partly related to longer conversion times and spontaneous late reversions, and not necessarily to drug effect.

The use of class 1C drugs in AF has a risk of induction of atrial flutter, as reported in the literature.[26-28] However, in this study, only 2 patients receiving flecainide, and 1 receiving placebo had this arrhythmia, with ventricular rates of <150 beats/min and without hemodynamic deterioration. It is likely that the resting condition of our patients was a natural obstacle to a possible 1:1 conduction. No ventricular proarrhythmic effects were observed in our patients.[29]

Maximal heart rate evaluated on Holter monitoring was reduced by the same amount with flecainide and amiodarone to an extent statistically superior to that with placebo. Furthermore, a progressive mean or maximal heart rate decrease was a common pattern in the hour before each conversion to sinus rhythm.

In 1 case with flecainide, an asymptomatic pause >9 seconds was observed immediately before resumption of sinus rhythm. Flecainide has a known depressive effect on sinus node automaticity and is relatively contraindicated in patients with sick sinus syndrome.[30] The aforementioned patient probably had sick sinus syndrome, and AF was an expression of a bradycardia-tachycardia syndrome.

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Electrocardiographic Changes and Arrhythmias After Cancer Therapy in Children and Young Adults

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Transient electrocardiographic changes and arrhythmias are known to be acute manifestations of cardiotoxicity secondary to cancer therapy with anthracyclines or cardiac irradiation. However, despite the known risk of late cardiac dysfunction in survivors of childhood cancer therapy, the risk of clinically important electrocardiographic abnormalities and arrhythmias after treatment is unknown. Standard 12-lead and 24-hour ambulatory electrocardiograms were recorded in 73 patients who received anthracyclines alone, 24 who received cardiac irradiation alone, and 27 who received both anthracyclines and cardiac irradiation. The mean age of the patients was 15 years. Mean cumulative anthracycline dose was 282 mg/m² in patients who received anthracyclines alone and 244 mg/m² in patients who received both anthracyclines and cardiac irradiation. Analysis of the 12-lead and 24-hour electrocardiograms demonstrated increased frequency of QTc prolongation, supraventricular premature complexes, supraventricular tachycardia, ventricular premature complexes, couplets and ventricular tachycardia (all p <0.001) when compared with an age-matched healthy population. Most patients had abnormalities limited to single supraventricular or ventricular premature complexes; however, potentially serious ventricular ectopy, including ventricular pairs and ventricular tachycardia, were noted in patients with cumulative doses >200 mg/m².

Electrocardiographic abnormalities and arrhythmias are not limited to the acute phase of treatment with anthracyclines and cardiac irradiation. Survivors of childhood malignancy who received anthracyclines or cardiac irradiation, or both, probably should undergo ambulatory electrocardiographic monitoring as part of their follow-up to detect potentially life-threatening arrhythmias.

(Am J Cardiol 1992;70:73-77)

At least 25% of patients who receive anthracyclines or cardiac irradiation during cancer therapy develop electrocardiographic abnormalities or arrhythmias.[1] The anthracyclines, doxorubicin and daunorubicin, are effective, frequently used agents with well-described acute and chronic cardiotoxicity, including ventricular dysfunction, pericarditis, electrocardiographic abnormalities and arrhythmias.[2-4] In addition to these toxicities, cardiac irradiation also causes accelerated coronary arteriosclerosis.[5-7] Electrocardiographic changes and arrhythmias include decreased QRS voltage, prolongation of the QT interval, T-wave inversion, ST-segment elevation or depression, and atrial and ventricular arrhythmias. In adults, these abnormalities are generally considered to be transient and of little clinical significance. Children develop cardiac toxicity at lower doses relative to body size than adults.[1,8] This increased sensitivity may place them at greater risk for the development of significant and persistent abnormalities. Neither the frequency nor the significance of chronic electrocardiographic changes or arrhythmias in children who receive anthracyclines, cardiac irradiation, or both, are known. We used 12-lead electrocardiography and 24-hour ambulatory electrocardiographic (Holter) monitoring to learn the prevalence of electrocardiographic changes and arrhythmias in survivors of childhood cancer.

METHODS

Patients: Patients who had completed prescribed courses of therapy for a malignancy that included anthracyclines or cardiac irradiation were asked to participate in the study. To eliminate the clinically insignificant transient acute electrocardiographic changes previously reported in adult patients, all patients had not had cardiotoxic therapy for ≥3 months before enrollment. All patients were clinically asymptomatic and without evidence of residual malignancy. Informed consent was obtained from the patient and, where appropriate, the parent. Approval for the study was obtained from the institutional review board.

One hundred thirty-four children and young adults (age 15 ± 4 years; range 7 to 32) participated in the study. Diagnoses included acute lymphoblastic leukemia (15), acute nonlymphocytic leukemia (10), Hodgkin's disease (21), non-Hodgkin's lymphoma (25), Wills' tumor (22), neuroblastoma (3), rhabdomyosarcoma (8), osteosarcoma (6), Ewing's sarcoma (6), other sarcomas (2), teratoma (1), and central nervous system tumors (15). Twelve of these patients (9%) were aged ≥21

Age (yr)	AV Block Type I	AV Block Type II	SVPCs	SVT	VPCs	Multiform VPCs	Couplets	VT
6–13	14/223 (6%)	0/223 (0%)	20/223 (9%)	0/223 (0%)	35/223 (16%)	0/92 (0%)	0/223 (0%)	0/223 (0%)
14–16	11/100 (11%)	1/100 (1%)	44/100 (44%)	0/100 (0%)	41/100 (41%)	10/100 (10%)	3/100 (3%)	3/100 (3%)
22–28	5/100 (5%)	0/100 (0%)	60/100 (60%)	2/100 (2%)	52/100 (52%)	11/100 (11%)	0/100 (0%)	1/100 (1%)
Age-adjusted normals	8 ± 2%	0.5 ± 0.5%	30 ± 3%	0.1 ± 0.1%	31 ± 3%	6 ± 1%	1.5 ± 0.8%	1.5 ± 0.8%

AV = atrioventricular; SVPCs = supraventricular premature complexes; SVT = supraventricular tachycardia; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

years at entry into the study. Time since last anthracycline administration or cardiac irradiation ranged from 3 months to 21 years. One hundred sixteen patients (87%) had completed therapy for at least 1 year before the time of testing. The mean time from last cardiotoxic agent for the entire population was 5 ± 4 years.

Seventy-three patients had received anthracyclines but no cardiac irradiation with a cumulative anthracycline dose of 282 ± 106 mg/m^2 (range 84 to 665). Four received >450 mg/m^2 of anthracyclines. Twenty-four received cardiac irradiation but no anthracyclines. Thirty-seven received both anthracyclines and cardiac irradiation (anthracycline dose 244 ± 65 mg/m^2).

Electrocardiography: Supine standard 12-lead electrocardiography was performed using a Marquette Case 12 electrocardiographic system and interpreted using age-specific criteria.[9]

Ambulatory electrocardiographic monitoring: Tracings were recorded for a single 24-hour period with a portable electrocardiographic cassette tape recorder (CardioTechcorder II), a 2-channel system with modified leads V$_1$ and V$_5$. The tapes were analyzed using a superimposition scanning technique with each recording reviewed by 2 operators. Printings of arrhythmias, extremes of heart rate, and representative strips from each study hour were produced for detailed analysis and review. The results of the ambulatory electrocardiograms were interpreted by a pediatric cardiologist and compared with published age-specific norms (Table I).[10-14]

Definitions: Twenty-four-hour average heart rate was defined as the total number of complexes recorded divided by the total recording time. Highest and lowest heart rate was defined as the fastest and slowest rate of 16 consecutive complexes. The following arrhythmias were defined using standard criteria: supraventricular premature complexes, ectopic atrial rhythm (rate 40 to 80 beats/min), accelerated ectopic atrial rhythm (rate 80 to 119 beats/min), supraventricular tachycardia (≥3 non-sinus complexes at a rate ≥120 beats/min), junctional rhythm, ventricular premature complexes, multiform and coupled ventricular premature complexes, accelerated idioventricular rhythm (≥3 complexes at a rate 60 to 119 beats/min), ventricular tachycardia (≥3 ventricular complexes at a rate >120 beats/min), first-degree atrioventricular (AV) block (PR interval >95th percentile for age), and second-degree AV block, Mobitz types I and II. PR, QRS and QT intervals were measured. The QT interval was corrected for heart rate using Bazett's formula: measured QT divided by the square root of the RR interval and reported as QTc.

Echocardiography: Within 24 hours of their electrocardiography, all patients underwent 2-dimensional echocardiography to measure left ventricular end-diastolic and end-systolic diameters in the minor axis. A shortening fraction of ≥0.28 was considered normal.[15]

Data analysis: Cumulative anthracycline doses were calculated by summing the total dose of doxorubicin in mg/m^2 plus two-thirds of the total daunorubicin dose in mg/m^2.[16] Means were reported with their associated standard deviations (mean ± standard deviation). The frequency of abnormal results between groups was compared using the chi-square statistic or Fisher's exact test. Comparison of means between groups was performed using a 2-tailed student t test. A p value <0.05 was considered significant.

RESULTS

Twelve-lead electrocardiography: Results are summarized in Table II. Eighty-eight patients (66%) had no abnormalities on 12-lead electrocardiography. Ectopic atrial rhythm was seen in 8 patients (6%) and a prolonged QTc interval of >0.44 was seen in 19 patients (range 0.45 to 0.50). The 14% prevalence of prolonged QTc was significantly greater (p <0.001) than expected. Abnormally flattened or inverted T waves were seen in 3 patients (2%). No patient had abnormal QRS voltages in the chest or limb leads.

Q waves of increased amplitude in leads II, III, aVF, and/or V$_6$ were found in 3% of the patients who had received anthracyclines alone and in 10% of the patients who had received cardiac irradiation. None of these patients had echocardiographic evidence of left ventricular or septal hypertrophy. Electrocardiograms had not been obtained before beginning therapy, so it cannot be determined whether these Q waves developed after therapy.

Ambulatory electrocardiography: RATE AND RHYTHM: The predominant rhythm was sinus in all patients. Brief episodes of ectopic and junctional rhythms were recorded in 5 patients. Daily heart rate was 88 ± 11 beats/min, sleeping heart rate 78 ± 14 beats/min, and the lowest and highest recorded heart rates 55 ± 10 beats/min and 161 ± 19 beats/min, respectively.

ATRIOVENTRICULAR BLOCK: Second-degree AV block, Mobitz type I (Wenckebach) was not observed in any patients who received <300 mg/m^2 of anthracyclines, but was detected in 5 of 32 (16%) (p <0.01) who received >300 mg/m^2 of anthracyclines and in 1 of 37 (3%) (p = not significant [NS] compared with <300 mg/m^2) who received both anthracyclines and cardiac

TABLE II 12-Lead Electrocardiographic Findings in Survivors of Childhood Cancer

	Normal ECG	Ectopic Atrial Rhythm	Right Ventricular Hypertrophy	Interventricular Conduction Delay	Deep Q Waves	Other
Anthracyclines (1–199 mg/m²)	12/14 (86%)	1/14 (7%)	0/14 (0%)	0/14 (0%)	1/14 (7%)	None
Anthracyclines (200–299 mg/m²)	17/28 (61%)	1/28 (4%)	0/28 (0%)	0/28 (0%)	1/28 (4%)	T-wave flattening or inversion (3); QTc > 0.44 (3)
Anthracyclines (300–399 mg/m²)	14/21 (67%)	1/21 (5%)	1/21 (5%)	0/21 (0%)	0/21 (0%)	Wolff-Parkinson-White (1); right-axis deviation (1); right atrial enlargement (1); QTc > 0.44 (2)
Anthracyclines (> 400 mg/m²)	6/10 (60%)	2/10 (20%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	QTc > 0.44 (3)
Cardiac irradiation	15/24 (63%)	2/24 (8%)	0/24 (0%)	2/24 (8%)	5/24 (21%)	QTc > 0.44 (3); right atrial enlargement (1)
Both anthracyclines and cardiac irradiation	24/37 (65%)	1/37 (3%)	1/37 (3%)	0/37 (0%)	1/37 (3%)	QTc > 0.44 (7)

ECG = electrocardiogram.

TABLE III Arrhythmias Detected by 24-Hour Electrocardiography in Survivors of Childhood Cancer

	Supraventricular Premature Complexes	Supraventricular Tachycardia	Ventricular Premature Complexes	Ventricular Couplets	Ventricular Tachycardia
Anthracyclines (1–199 mg/m²)	8/14 (57%)*	0/14 (0%)	4/14 (29%)	0/14 (0%)	0/14 (0%)
Anthracyclines (200–299 mg/m²)	17/28 (61%)*	2/28 (7%)*	9/28 (36%)	1/28 (4%)†	0/28 (0%)
Anthracyclines (300–399 mg/m²)	16/21 (76%)*	0/21 (0%)	14/21 (67%)*	0/21 (0%)	0/21 (0%)
Anthracyclines (≥ 400 mg/m²)	5/10 (50%)*	0/10 (0%)	7/10 (70%)*	1/10 (10%)†	0/10 (0%)
Cardiac irradiation	15/24 (63%)*	1/24 (4%)*	12/24 (50%)*	0/24 (0%)	1/24 (4%)†
Both anthracyclines and irradiation	27/37 (73%)*	0/37 (0%)	23/37 (62%)*	3/37 (8%)*	3/37 (8%)*
All patients	(66%)*	(2%)*	(52%)*	(4%)*	(3%)*

*p < 0.001; †p < 0.01 (probabilities compared with that in normal subjects).

irradiation. One or 2 episodes each of Mobitz type II second-degree AV block was recorded in 2 of 42 patients (5%) who received <300 mg/m² of anthracyclines, compared with 1 of 31 (3%) (p = NS) who received >300 mg/m² of anthracyclines. Two of the 61 patients (3%) (p = NS compared with <300 mg/m²) who received cardiac irradiation developed Mobitz type II second-degree AV block. Both had received anthracyclines. No symptoms were reported during any episodes of AV block.

MAXIMUM CORRECTED QT INTERVAL: Corrected QT interval was ≥0.48 in 19 of 134 patients (14%). There was no significant difference in mean anthracycline or irradiation doses between patients with or without prolongation of their corrected QT intervals.

SUPRAVENTRICULAR ARRHYTHMIAS: Although supraventricular premature complexes were more common in our study population (p <0.001) than in age-matched normal subjects (Table I), there were no dose-related differences in the study population (Table III). The number of supraventricular complexes recorded in the 24-hour period ranged from 0 to 552, with 18 patients having >10. Two patients (1.5%) each had 1 episode of

nonsustained supraventricular tachycardia at rates of 120 and 142 beats/min. The duration of supraventricular tachycardia was 3 beats in one of these patients and 11 beats in the other. No symptoms were reported during these episodes.

VENTRICULAR ARRHYTHMIAS: The prevalence of ventricular ectopy did not differ from normal in patients who had received <300 mg/m² of anthracyclines. Patients who received >300 mg/m² of anthracyclines, cardiac irradiation without anthracyclines, or both anthracyclines and cardiac irradiation, had an increased prevalence of ventricular ectopy (all p <0.001) compared with results in age-matched normal subjects (Tables I and III). The number of ventricular premature complexes recorded in 24 hours ranged from 0 to 126, with 8 of 134 patients (6%) having >10 single ventricular premature complexes. The complexes were multiform in 2 of 42 patients (5%) (p = NS compared with normal) who received <300 mg/m² of anthracyclines, in 6 of 31 patients (19%) (p = NS compared with normal) who received >300 mg/m², in 2 of 24 patients (8%) (p = NS compared with normal) who received cardiac irradiation without anthracyclines, and in 6 of 37 patients

(16%) (p = NS compared with normal) who received both anthracyclines and cardiac irradiation.

Single ventricular pairs were recorded in 1 of 42 patients (2%) who received <300 mg/m^2 of anthracyclines, 1 of 31 patients (3%) who received >300 mg/m^2, no patient who received cardiac irradiation without anthracyclines, and 3 of 37 patients (8%) who received both anthracyclines and cardiac irradiation. The coupling interval between the 2 ectopic complexes ranged from 0.29 to 0.53 seconds.

Nonsustained ventricular tachycardia (3 to 6 beats) at rates of 168, 180 and 181 beats/min was recorded in 3 patients. One patient had a 55 beat run of an accelerated ventricular rhythm (rate 120 beats/min). Ages ranged from 13.2 to 24.3 years. Times since completion of therapy were 0.6, 0.8, 5 and 13 years. Patient diagnoses included: Hodgkin's disease (2), non-Hodgkin's lymphoma (1) and neuroblastoma (1). One patient with ventricular tachycardia had received irradiation alone. The others had received both anthracyclines (cumulative doses ranged from 141 to 300 mg/m^2) and mediastinal irradiation. The episodes occurred while patients were reportedly awake and engaged in sedentary activities, i.e., doing homework, watching television. Patients noted no symptoms during the episodes of ventricular tachycardia. Twelve-lead electrocardiograms were normal in 3 patients; 1 patient had right-axis deviation (QRS axis +117). None of the patients had a QTc >0.44 on 12-lead electrocardiography. All 4 patients had normal left ventricular shortening fractions (range 0.31 to 0.36). None of the patients had mitral valve prolapse on echocardiography.

Echocardiography: Mean left ventricular shortening fraction was 0.34 ± 0.04 in patients who received <300 mg/m^2 of anthracyclines, 0.32 ± 0.05 in patients who received >300 mg/m^2 of anthracyclines, 0.34 ± 0.04 in patients who received cardiac irradiation without anthracyclines, and 0.32 ± 0.04 in patients who received both anthracyclines and cardiac irradiation. There was no difference in mean shortening fractions across the groups. Shortening fraction was <0.28 in 2 patients who received <300 mg/m^2, in 5 patients who received >300 mg/m^2 of anthracyclines, in 1 patient who received cardiac irradiation without anthracyclines, and in 1 patient who received both anthracyclines and cardiac irradiation. Abnormal shortening fraction did not correlate with findings on either standard or 24-hour electrocardiography.

DISCUSSION

Previous studies: Decreased QRS voltage, T-wave flattening and inversion, ST-segment elevation or depression, prolongation of the QT interval, and AV and bundle branch block are reported to be common electrocardiographic manifestations of acute cardiac toxicity during and shortly after treatment with anthracyclines[17-22] or cardiac irradiation, or both.[23] Arrhythmias, including supraventricular and ventricular premature complexes, junctional rhythm, and supraventricular and ventricular tachycardias have also been reported.[1,24] Some studies have suggested that in adult patients, the electrocardiographic changes and arrhythmias associated with anthracycline cardiac toxicity resolve within 1 month of cessation of treatment,[24,25] are of little clinical significance, and are not predictive of the future development of congestive heart failure or death.[25,26] There are other reports in adult patients of sudden death, presumably secondary to an arrhythmia, during anthracycline infusion or shortly after treatment with anthracyclines or mediastinal irradiation, or both.[27,28]

Studies in pediatric patients are limited. Steinherz and Steinherz[29] reported the long-term follow-up of 100 children who had received anthracyclines. Three developed clinical symptoms of congestive heart failure and another 13 had abnormal echocardiograms. One patient who had not had a previously documented arrhythmia died suddenly, and 2 patients who had previously documented ventricular arrhythmias died secondary to their arrhythmias. In another study, Lipshultz et al[30] detected nonsustained ventricular tachycardia in 5% of late survivors of childhood malignancy. Their mean cumulative doxorubicin doses were 484 mg/m^2. All patients in whom ventricular tachycardia was detected had severe systolic dysfunction on echocardiography, although, in some patients, ventricular tachycardia preceded the onset of symptomatic congestive heart failure.

Present study: COMPARISON WITH PREVIOUS STUDIES: Our study confirms the association of electrocardiographic abnormalities and arrhythmias including AV block, prolonged corrected QT interval, and supraventricular and ventricular arrhythmias with cancer therapy. Unlike prior studies in adults that report transient early arrhythmias usually limited to the first month,[24,25] our patients' abnormalities were detected beyond the acute phase of therapy. This suggests that children receiving anthracyclines and cardiac irradiation are more likely to develop chronic electrocardiographic changes and late arrhythmias. Previous studies in adults have not used long-term ambulatory electrocardiography, however, and may have underestimated the frequency of arrhythmias.

In our study, although there was a relation between prevalence of ventricular arrhythmias and dose, ventricular arrhythmias were detected in patients receiving cumulative anthracycline cumulative doses as low as 200 mg/m^2. Unlike the study by Lipshultz, we detected nonsustained ventricular tachycardia in patients who had received what is generally considered to be "safe" (<300 mg/m^2) doses of anthracyclines and in patients without overt ventricular systolic dysfunction.

SIGNIFICANCE OF ELECTROCARDIOGRAPHIC CHANGES AND ARRHYTHMIAS: In most of the patients, minor abnormalities were found that were of little clinical significance. Potentially serious electrocardiographic changes and arrhythmias were noted in some patients.

In our study, a QTc ≥0.48 on 24-hour ambulatory electrocardiography monitoring was seen in 14% of patients who received either anthracyclines, cardiac irradiation or both. This finding may indicate a substrate of electrical instability, making the presence of even normal numbers of ventricular premature complexes a more potentially threatening situation.

Q waves of increased amplitude were detected in patients who had received cardiac irradiation and may in-

dicate myocardial ischemia or the presence of chronically fibrotic areas of myocardium, or both.

Potentially serious ventricular arrhythmias, including ventricular tachycardia, occurred more often in patients receiving both anthracyclines and irradiation than in patients receiving either anthracyclines or irradiation alone, confirming previous observations that cardiac irradiation lowers the dose level at which anthracycline cardiotoxicity develops.[1,6] The significance of ventricular ectopy in these patients is unknown. For this reason, we have elected not to treat these arrhythmias in clinically asymptomatic patients. All patients with supraventricular tachycardia, ventricular couplets or ventricular tachycardia were referred to a pediatric cardiologist for full evaluation and are currently being followed. The remaining patients are continuing with their routine oncologic follow-up which will include serial ambulatory electrocardiographic monitoring. It is too soon to comment on progression of arrhythmias or clinical symptomatology in either of these groups.

Study limitations: Limitations of our study include the lack of 12-lead or 24-hour electrocardiograms obtained before beginning therapy to assess for preexisting abnormalities. Because studies were not systematically obtained during therapy, we cannot determine if patients had significant electrocardiographic changes or arrhythmias at the time of therapy and cannot evaluate whether arrhythmias occurring acutely during treatment are predictive of persistent or recurrent arrhythmias after treatment. An additional limitation is the relatively short period of monitoring for arrhythmias (24 hours). Patients with ventricular arrhythmias have arrhythmias that occur sporadically with a marked variability in the frequency of arrhythmias during repeated periods of long-term ambulatory electrocardiographic monitoring. Our study may therefore underestimate the prevalence of arrhythmias in survivors of childhood cancer.

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Stimulation of the Summit of the Right Ventricular Aspect of the Ventricular Septum During Orthodromic Atrioventricular Reentrant Tachycardia

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Application of ventricular premature complexes (VPCs) from the right ventricular (RV) apex during orthodromic atrioventricular (AV) reentrant tachycardia has limitations both in the ability to shorten the succeeding atrial cycle length and in helping to identify accessory pathway location. Stimulation from the summit of the RV aspect of the septum during AV reentrant tachycardia was investigated as a new technique to improve the diagnostic utility of applying VPCs during AV reentrant tachycardia. VPCs were induced during AV reentrant tachycardia at 10 ms decrements in patients with left free wall (n = 15), posteroseptal (n = 5), and right free wall (n = 3) accessory pathways from the RV apex and then from the summit of the RV septum. When the His was refractory, shortening of the atrial cycle length was noted in 13% of patients with left free wall pathways, in 60% of patients with posteroseptal pathways, and in 100% of patients with right free wall pathways with VPCs from the RV apex, and in 47, 100 and 100%, respectively, with VPCs from the summit of the septum. When all VPCs were considered, there was a significant shortening of the atrial cycle length in 67% of patients with left free wall pathways when stimulated from the RV apex, which increased to 93% with summit stimulation. An extrastimulus applied on or after the His effected a significant shortening of the atrial cycle length in no patients with left free wall pathways. The mean maximal shortening of the atrial cycle length when the His was refractory was 4 ± 11 and 9 ± 13 ms for left free wall pathways, 29 ± 30 and 40 ± 11 ms for posteroseptal pathways, and 35 ± 15 and 53 ± 35 ms for right free wall accessory pathway from the apex (p = 0.006) and summit (p = 0.0002), respectively. Stimulation of the summit of the RV septum improves the ability of VPCs to shorten the atrial cycle length during AV reentrant tachycardia.

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The diagnosis of orthodromic atrioventricular (AV) reentrant tachycardia using a bypass tract can be confirmed by stimulating the ventricle when the His bundle is refractory. When the His is refractory, ventriculoatrial conduction can only be negotiated via an accessory pathway; thus, advancement of the next atrial electrogram by a ventricular premature complex (VPC) confirms the presence of an accessory pathway. Furthermore, if the sequence of atrial activation remains the same as that observed during the tachycardia, the tachycardia circuit most likely includes the accessory pathway as the retrograde limb. Application of VPCs is generally performed from the right ventricular (RV) apex. Applicability of this maneuver depends on the ability of the VPC to engage and reset the tachycardia. Available data[1–3] suggest that stimulation from the RV apex has only limited applicability for patients with left free wall accessory pathways, since during tachycardia the pathway may be engaged orthodromically before an RV extrastimulus crosses the septum to activate the accessory pathway. This study assesses whether application of VPCs during tachycardia at the summit of the RV aspect of the septum (closer to the tachycardia circuit) increases the diagnostic yield. In addition, we tested whether stimulation of the RV summit may help differentiate posteroseptal from right and left free wall accessory pathways.

METHODS

Inclusion criteria for this study were: (1) patients undergoing electrophysiologic studies in the drug free state between November 1988 and October 1990; (2) the presence of inducible orthodromic AV reentrant tachycardia via a single accessory pathway; and (3) application of VPCs during tachycardia from both the RV apex and summit of the RV aspect of the septum. The inclusion criteria were met by 32 patients, 9 of whom were excluded because of capture of the atrium during stimulation from the summit of the septum (n = 3; Figure 1), excessive spontaneous variation in the tachycardia cycle length (>15 ms beat to beat variation; n = 1), or incomplete data acquisition due to technical factors (n = 5). Twenty three patients (15 men, 8 women; mean age 33 ± 13 years) form the study population. All patients had symptomatic episodes of supraventricular tachycardia.

After written informed consent was obtained, all patients underwent standard electrophysiologic studies in the nonsedated, fasting state after cardiac medications had been stopped for ≥5 half-lives. Quadripolar cathe-

ters (6F USCI) were positioned in the high right atrium, His bundle region and right ventricle through sheaths placed in the femoral vein. A multipolar electrode catheter was positioned in the coronary sinus through a sheath placed in either the right internal jugular or left subclavian vein. Electrocardiographic leads I, II, aVF, and V_1 and the intracardiac electrograms (bandpass filters 30 to 250 Hz) were displayed on an oscilloscope and recorded at a paper speed of 100 mm/s. Pacing was performed with a programmable stimulator (Bloom Associates, Reading, Pennsylvania) using rectangular stimuli at twice the diastolic threshold with a stimulus duration of 2 ms. Standard techniques for the induction of supraventricular tachycardia were used.[4] If supraventricular tachycardia was not induced in the baseline state, intravenous isoproterenol (1 to 2 µg/min) was begun and tachycardia was induced with programmed stimulation. AV junctional reentrant tachycardia was ruled out as the mechanism for tachycardia by the presence of (1) a ventriculoatrial time during tachycardia of >61 ms in the His bundle recording[5] and eccentric retrograde atrial activation during tachycardia, or (2) by the ability to preexcite the atrium during tachycardia with a VPC applied when the His bundle was refractory.

Mapping of retrograde atrial activation was performed during orthodromic AV reentrant tachycardia in the right atrium with a modified Brockenbrough catheter and in the coronary sinus with a multipolar electrode catheter. Left free wall accessory pathways were defined by the earliest retrograde atrial activation occurring within the coronary sinus. If the earliest activation was within 5 mm of the coronary sinus os, the pathway was designated posteroseptal. If the earliest activation was 5 mm to 3 cm from the os, the pathway was defined as left posterior. If the earliest activation was distal to this point, the pathway was labeled left lateral. Because there was no difference in the data for left posterior versus lateral pathways, they were included together in the data analysis. Right-sided pathways were defined by the earliest retrograde atrial activation occurring in the right atrium.

During orthodromic AV reentrant tachycardia, diastole was scanned with single VPCs starting in late diastole and then at 10 ms decrements. Stimulation was first performed from the RV apex at twice the diastolic threshold. Stimulation was then repeated from the His bundle catheter, in effect stimulating the summit of the RV septum. The stimulating current was increased until ventricular capture was obtained. If capture could not be obtained from the standard His bundle recording position, the catheter was advanced slightly to make contact with the RV septal myocardium.

VPCs were applied from both the RV apex and summit of the RV aspect of the septum to examine the ability to advance the succeeding atrial electrogram. Ideally, while using this technique, VPCs need to be applied while the His bundle is refractory.[1] The minimal normal anterograde His to ventricular conduction time is 35 ms.[6] Assuming a similar minimal retrograde interval, a VPC applied 35 ms before the His deflection should arrive when the His bundle is already committed. This is clearly a conservative figure since intraventricular conduction time is excluded. For purposes of this study, we accepted extrastimuli up to 35 ms preceding the His bundle (i.e., an SH interval of 35 ms) as occurring when the His bundle is definitely refractory.

The following intervals were defined and recorded (Figure 2): (1) The VS interval was defined as the interval from the preceding ventricular depolarization to the stimulus artifact. (2) The VH interval was defined as the interval from the preceding ventricular depolarization to the His bundle potential. If the His bundle deflection was obscured by the pacing artifact, the VH interval was obtained from the complex just preceding the VPC. (3) The SH interval represents the interval from the stimulus to the His deflection and was calculated by subtracting the VS interval from the VH interval. Positive numbers indicate the stimulus preceded the His bundle and negative numbers indicate the stimulus followed the His. (4) The change in atrial cycle length induced by the VPC was recorded. The shortening of the atrial cycle length was considered significant only if this parameter was ≥15 ms. (5) The shortening of the atrial cycle length was adjusted for the degree of pre-

FIGURE 1. Simultaneous recordings of surface electrocardiographic leads V_1, I, II and aVF with intracardiac recordings from high right atrium (HRA), distal (HBEd) and proximal (HBEp) His bundle electrograms, and proximal (CSp) and distal (CSd) coronary sinus in patient with posteroseptal accessory pathway. Attempt at inducing premature ventricular complex from summit of right ventricular septum is demonstrated. There is no ventricular capture, but sequence of retrograde atrial activation is changed from that during tachycardia. Note that atrial electrogram in coronary sinus appears on time (arrow), despite advancement of atrial electrogram in high right atrium recording. Observed shortening of atrial cycle length is due to capture of low septal right atrium at high current strength used.

maturity of the VPCs by subtracting the SH interval from the observed change in atrial cycle length. Thus, an early VPC (large S4 interval) that advanced the atrial electrogram by 20 ms had a smaller adjusted shortening of the atrial cycle length than a late VPC (large S4 interval) that advanced the succeeding atrial electrogram by 20 ms. Miles et al[7] examined only the degree of prematurity required to shorten the atrial cycle length without accounting for the magnitude of the change in the atrial cycle length. Thus, the adjusted shortening of the atrial cycle length was designed to account for both the degree of prematurity (SH interval) and the magnitude of the change in the atrial cycle length. (6) The preexcitation index was calculated as described by Miles et al[7] as the difference between the tachycardia cycle length and the longest VS interval associated with a significant shortening of the atrial cycle length.

Statistical analysis: Two separate analyses were performed. The first analysis examined only the data for an SH interval ≤35 ms, when the His bundle was definitely committed and refractory. The second analysis evaluated the data for all SH intervals, which is an analysis that has been used previously.[7] In this analysis, the His bundle may or may not have been refractory. However, to ensure that any observed shortening of the atrial cycle length was secondary to conduction through the bypass tract, we required that the sequence of retrograde atrial activation be identical to that during the tachycardia. All data are presented as mean ± standard deviation. Group means for each of the accessory pathway

locations were compared using an analysis of variance. Scheffe's procedure was used to compare the differences among the 3 groups when a significant result was obtained. Repeated-measures analysis of variance was used to compare the means within each group. Categoric data were evaluated using an exact binomial test for correlated proportions. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Baseline characteristics of the patients are depicted in Table I.

Stimulation when His bundle is refractory (SH interval ≤35 ms): POSTEROSEPTAL ACCESSORY PATHWAYS: A significant shortening of the atrial cycle length was found in 3 of the 5 patients with posteroseptal pathways with RV apical stimulation and in all patients when stimulated from the summit of the septum (Figure 3). One of the patients who had no atrial preexcitation when VPCs were applied from the RV apex had a rapid tachycardia (cycle length 245 ms) and the maximal SH interval achieved was only 15 ms because of ventricular refractoriness. The other patient had a tachycardia cycle length of 320 ms but the maximal SH interval achieved was only 10 ms because of tachycardia termination. In this patient, the maximal SH interval achieved with VPCs from the summit of the RV septum was 0 ms, but this extrastimulus which was coincident with the His deflection advanced the succeeding atrial electrogram by 25 ms. The mean induced shortening of the atrial cycle length was 29 ± 30 ms (range 30 to 70)

FIGURE 2. Simultaneous recordings of surface electrocardiographic leads V_1, I, II and aVF with intracardiac recordings from high right atrium (HRA), distal (HBEd) and proximal (HBEp) His bundle electrograms, and coronary sinus (CS) in patient with left free wall accessory pathway. Single ventricular extrastimulus from right ventricular apex *(arrow)* during tachycardia does not change atrial cycle length (290 ms). VH and VS intervals are also displayed. SH interval is calculated as difference between VH and VS intervals. SH interval is 40 ms.

when VPCs were applied at the RV apex, and 40 ± 11 ms (range 25 to 55) when they were applied at the summit of the RV septum (p = not significant [NS]). VPCs applied on or after the inscription of the His potential resulted in shortening of the atrial cycle length in 4 of 5 patients when applied from the summit of the septum and in only 2 of 5 patients when applied from the RV apex. Figure 4 shows a VPC applied from the RV apex 15 ms before the onset of the His potential with no change in the atrial cycle length. In Figure 5, when the VPC is applied from the summit of the RV septum 15 ms after the onset of the His potential, there is a 30 ms shortening of the atrial cycle length.

RIGHT FREE WALL ACCESSORY PATHWAYS: All 3 patients with right free wall pathways had a significant shortening of the atrial cycle length when extrastimuli were induced from either the RV apex or the summit of the septum. The mean induced shortening of the atrial cycle length was 35 ± 15 ms (range 20 to 50) when VPCs were applied at the RV apex, and 53 ± 33 ms (range 15 to 75) when applied at the summit of the septum (p = NS). VPCs applied on or after the inscription of the His potential resulted in shortening of the atrial cycle length in only 1 patient when applied from the summit of the septum and in 2 of 3 patients when applied from the apex.

LEFT FREE WALL ACCESSORY PATHWAYS: With an SH interval ≤35 ms, only 2 patients (13%) with left free wall pathways had a significant shortening of the atrial cycle length during stimulation from the RV apex (Figure 3). In contrast, with stimulation from the summit of the RV septum, 6 patients (an additional 5) showed ad-

Age (yr) & Sex	Pathway Location	Concealed	TCL (ms)	Ablation Method
15 M	Left lateral	0	300	
16 F	Left lateral	0	270	
19 F	Left lateral	+	320	Surgical
21 M	Left lateral	+	290	
25 M	Left lateral	0	395	
29 M	Left lateral	0	380	Surgical
33 M	Left lateral	+	300	Surgical
36 M	Left lateral	+	280	
39 M	Left lateral	0	320	
42 F	Left lateral	0	300	
53 M	Left lateral	+	290	
19 M	Left posterior	0	405	Surgical
28 M	Left posterior	0	380	
29 F	Left posterior	0	405	
70 M	Left posterior	0	380	
26 M	Posteroseptal	0	245	Catheter
28 F	Posteroseptal	0	290	
37 F	Posteroseptal	0	325	Catheter
42 M	Posteroseptal	+	310	
31 M	Posteroseptal	0	320	Catheter
29 M	Right free wall	0	305	Surgical
34 F	Right free wall	0	450	
53 F	Right free wall	0	315	

TABLE I Baseline Characteristics of the 23 patients in the Study

Patients who underwent successful surgical or catheter ablation procedures are indicated.
TCL = tachycardia cycle length.

FIGURE 3. Diagnostic use of applying ventricular premature complexes from right ventricular apex, summit of right ventricular septum, and both during orthodromic atrioventricular reentrant tachycardia. For patients with left free wall accessory pathways, diagnostic use is displayed when extrastimuli are applied when His bundle is refractory (SH ≤35 ms) and when His bundle is not necessarily refractory (ALL SH). For patients with posteroseptal (PS) and right free wall accessory pathways, there was no difference in diagnostic use, whether extrastimuli were applied when His bundle was or was not necessarily refractory. ΔA = significant shortening of atrial cycle length.

FIGURE 4. Simultaneous recordings of surface electrocardiographic leads V_1, I, II and aVF with intracardiac recordings from high right atrium (HRA), proximal His bundle electrograms (HBEp), and proximal (CSp) and distal (CSd) coronary sinus in patient with posteroseptal accessory pathway. Single ventricular extrastimulus applied at the right ventricular apex (RVA) (arrow) during tachycardia does not change atrial cycle length. SH interval is 10 ms.
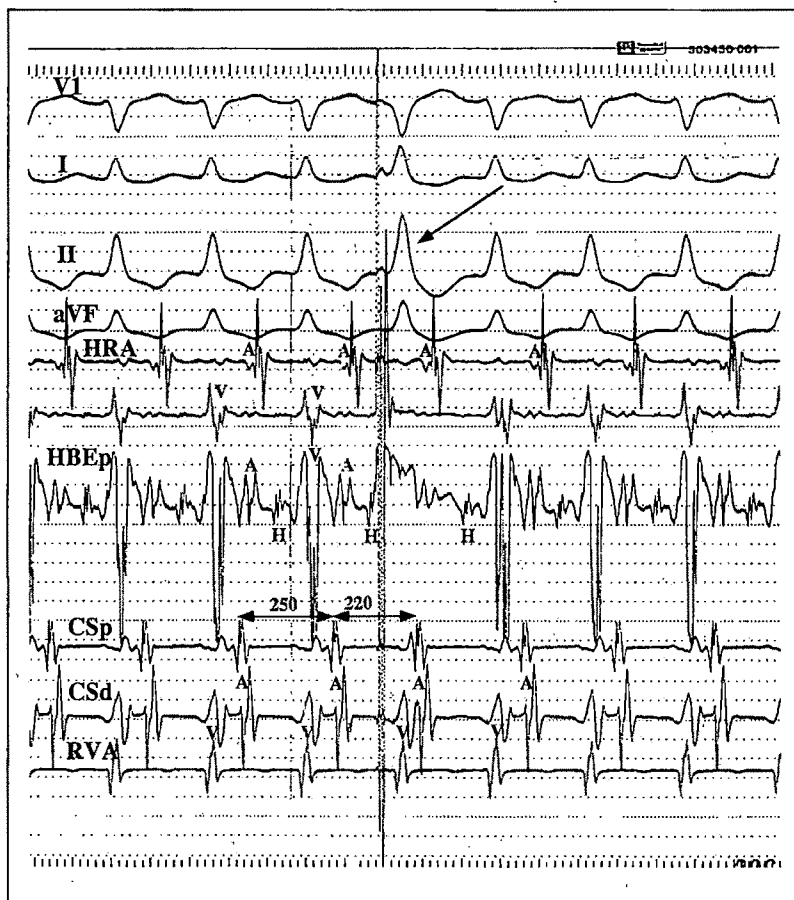
FIGURE 5. Simultaneous recordings of surface electrocardiographic leads V_1, I, II and aVF with intracardiac recordings from high right atrium (HRA), proximal His bundle electrograms (HBEp), and proximal (CSp) and distal (CSd) coronary sinus in same patient as in Figure 4. Single ventricular extrastimulus applied at summit of right ventricular septum during tachycardia shortens atrial cycle length by 30 ms. SH interval is −20 ms. Stimulus is applied 20 ms after inscription of His potential. RVA = right ventricular apex.

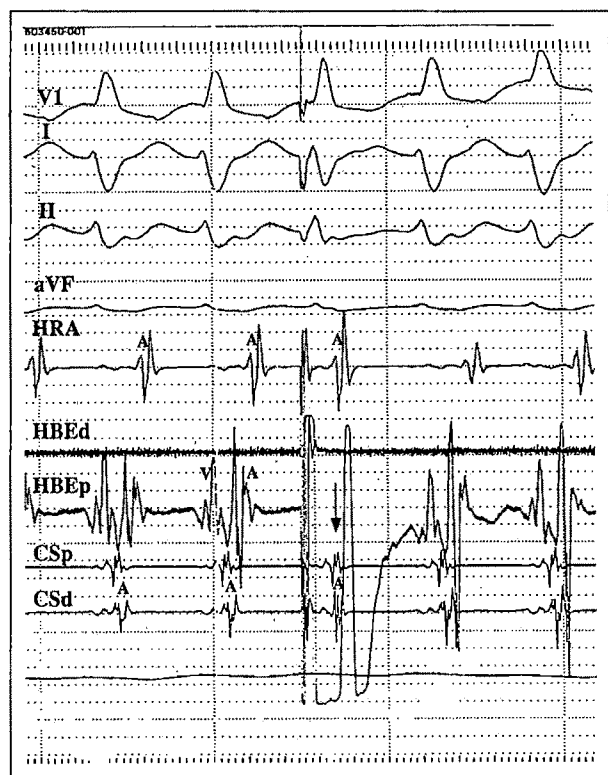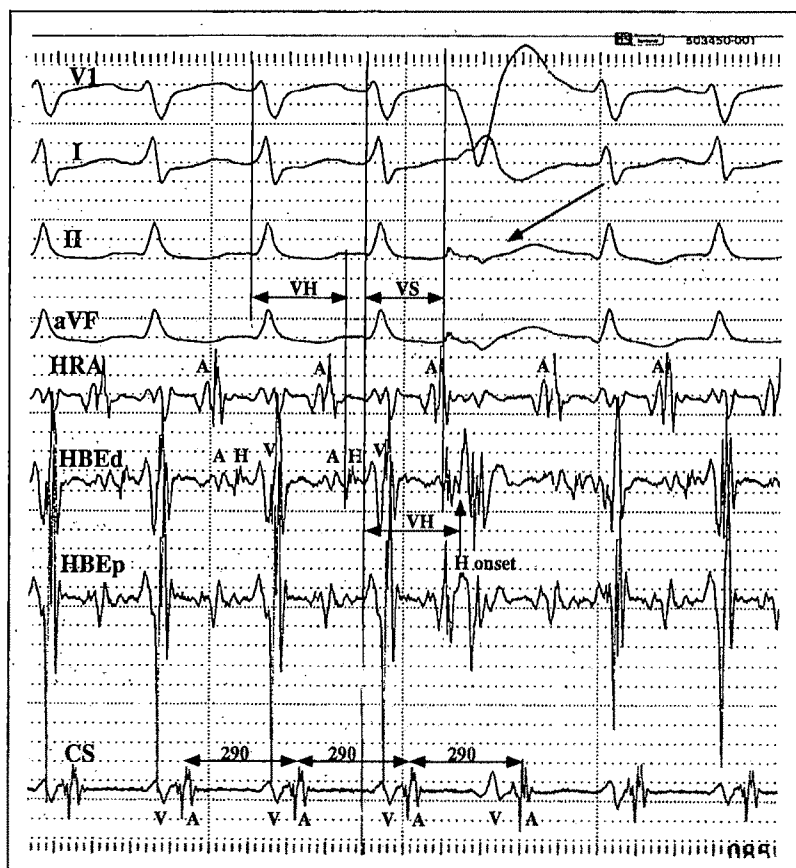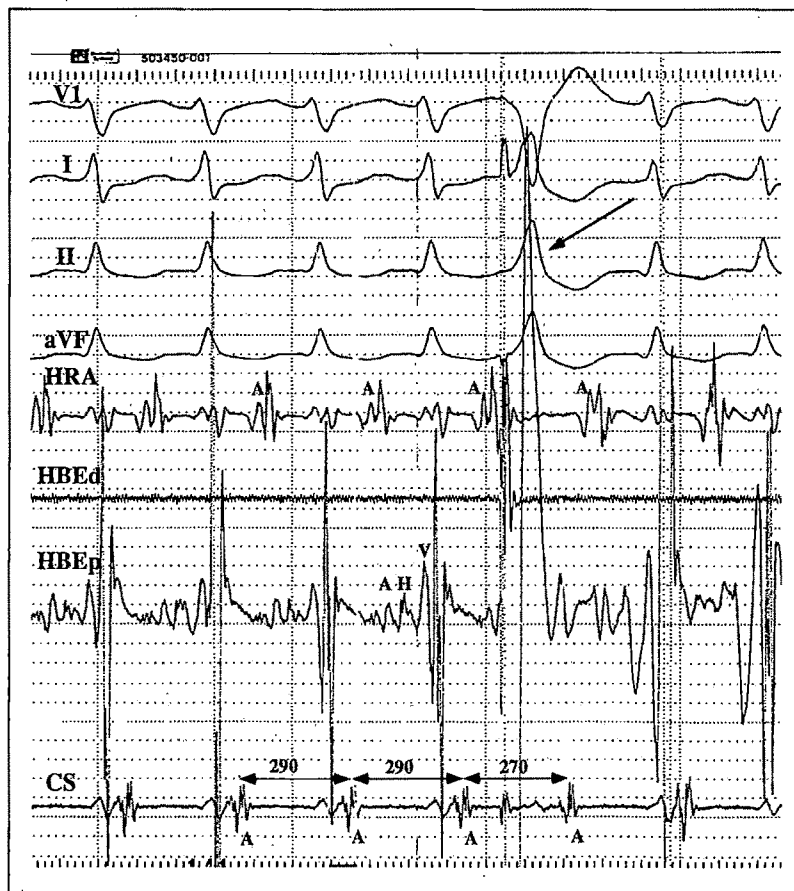FIGURE 6. Simultaneous recordings of surface electrocardiographic leads V_1, I, II and aVF with intracardiac recordings from the high right atrium (HRA), distal (HBEd) and proximal (HBEp) His bundle electrograms, and coronary sinus (CS) in same patient as in Figure 2. Single ventricular extrastimulus applied at summit of right ventricular septum (arrow) shortens atrial cycle length by 20 ms. SH interval is 30 ms.

vancement of the next atrial depolarization (Figure 3). Figures 2 and 6 demonstrate a typical case in which a VPC applied from the RV apex failed to shorten the atrial cycle length and a VPC applied from the summit of the RV septum did. Thus, application of VPCs from both the summit of the RV septum and the RV apex significantly improved the diagnostic yield of this maneuver (p <0.05) in patients with left free wall pathways. Nevertheless, 8 patients (53%) demonstrated no significant shortening of the atrial cycle length when VPCs were applied from either site with an SH interval ≤35 ms. The mean induced shortening of the atrial cycle length was 4 ± 11 ms when VPCs were applied at the RV apex, and 9 ± 13 ms when VPCs were applied at the summit of the septum. The maximal shortening of the atrial cycle length noted while the His bundle was refractory was 20 to 40 ms when VPCs were applied from the RV apex and 15 to 30 ms from the summit of the septum. The mean tachycardia cycle lengths for the patients who had atrial preexcitation when VPCs when applied from the summit of the septum was 351 ± 44 ms, and for patients who did not have atrial preexcitation it was 327 ± 52 ms (p = NS). An SH interval of 30 to 35 ms was achieved in all patients with VPCs from the RV apex, and in 13 of 15 patients with VPCs from the summit of the RV septum. One of these 2 patients with a maximal SH interval <30 ms had atrial preexcitation.

The mean shortening of the atrial cycle length among the 3 accessory pathway locations were significantly different (p = 0.006 for the RV apex and p = 0.0002 for the summit of the septum). However, further analysis revealed no significant difference between posteroseptal and right free wall pathways. There were no significant differences in the shortening of the atrial cycle lengths obtained by VPCs applied from the RV apex versus the summit of the RV septum for each accessory pathway location. When the data were analyzed taking into account the fact that an SH interval of 30 to 35 ms was not attained in all patients (using the adjusted shortening of the atrial cycle length) identical results were obtained.

No shortening of the atrial cycle length was noted when the VPC was applied on or after the inscription of the His recording (i.e., an SH interval ≤0) in patients with left free wall pathways. In contrast, a significant shortening of the atrial cycle length was noted in all patients with posteroseptal pathways and in 2 of 3 patients with right free wall pathways with VPCs applied on or after the inscription of the His recording from both RV sites.

Stimulation when His bundle is not necessarily refractory (all SH intervals): POSTEROSEPTAL AND RIGHT FREE WALL ACCESSORY PATHWAYS: When VPCs resulting in SH intervals >35 ms were included for analysis, there was no change in the number of patients with posteroseptal or right free wall pathways having a significant shortening of the atrial cycle length for either RV stimulation site. The maximal shortening of the atrial cycle length in patients with posteroseptal pathways was 36 ± 36 ms from the RV apex and 44 ± 14 ms from the summit of the septum (p = NS). These were associ-

ated with SH intervals of 30 ± 22 and 21 ± 24 ms, respectively (p = NS). The maximal shortening of the atrial cycle length in patients with right free wall pathways was 48 ± 12 ms from the apex and 63 ± 44 ms from the summit (p = NS). These were associated with SH intervals of 40 ± 44 and 38 ± 37 ms, respectively (p = NS).

LEFT FREE WALL ACCESSORY PATHWAYS: The atrial electrogram could not be advanced by a VPC applied at the RV apex in 5 patients (maximal SH intervals achieved 30 to 70 ms). When VPCs were applied at the summit of the septum, the atrial electrogram could not be advanced in 4 patients (maximal SH intervals achieved 10 to 55 ms). With use of both sites, significant shortening of the atrial cycle length was noted in 14 of 15 patients with left free wall pathways (Figure 3). Thus, a significant shortening of the atrial cycle length could not be obtained in only 1 patient who had a left lateral accessory pathway and a tachycardia cycle length of 290 ms. In this patient, the maximal SH interval obtained from VPCs applied at the RV apex was 70 ms and with VPCs from the summit of the septum it was 45 ms. The maximal shortening of the atrial cycle length observed in these patients was 24 ± 23 ms from the apex and 37 ± 35 ms from the summit of the septum (p = NS). These were associated with SH intervals of 63 ± 27 and 62 ± 36 ms, respectively (p = NS). The tachycardia cycle lengths for patients who demonstrated atrial preexcitation were 348 ± 50 and 343 ± 51 ms
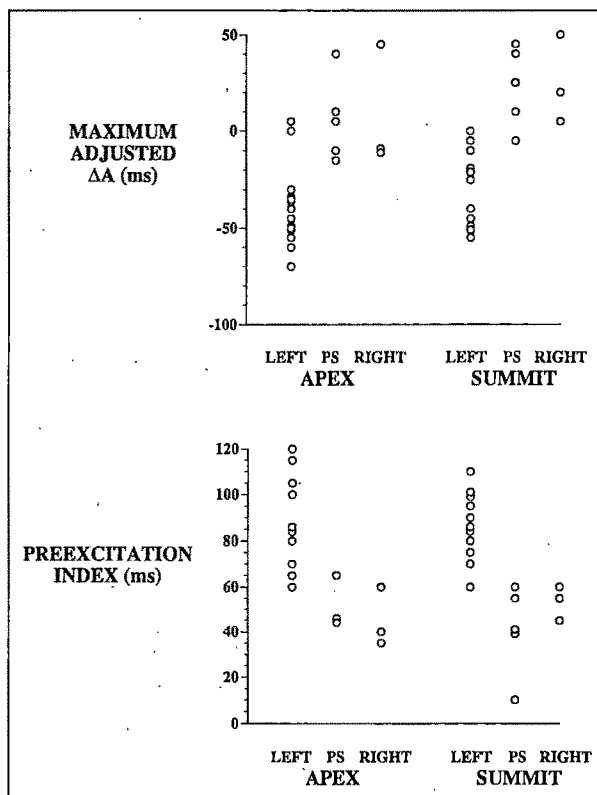
FIGURE 7. Maximum adjusted shortening of atrial cycle length (ΔA) and preexcitation index plotted for patients with left free wall (LEFT), posteroseptal (PS) and right free wall (RIGHT) accessory pathways when extrastimuli were applied at right ventricular apex (APEX), and summit of right ventricular septum (SUMMIT).

versus 314 ± 42 and 318 ± 42 ms for those that did not (p = NS) when VPCs were applied from the RV apex and summit of the septum, respectively.

No significant differences were noted among the maximal shortening of the atrial cycle lengths for each of the accessory pathway locations. However, when the shortening of the atrial cycle lengths were adjusted for the variable prematurity of the VPCs that achieved the maximal shortening of the atrial cycle length (using the adjusted shortening of the atrial cycle length), several findings were noted (Figure 7). For patients with left-sided accessory pathways, the adjusted shortening of the atrial cycle length was −39 ± 20 ms for VPCs applied from the RV apex and −25 ± 20 ms from the summit of the septum (p <0.05). The negative numbers indicate that earlier VPCs were required to advance the succeeding atrial electrogram by smaller amounts. For patients with posteroseptal pathways, the adjusted shortening of the atrial cycle length was 6 ± 22 ms for extrastimuli applied from the RV apex and 23 ± 21 ms from the summit of the septum (p = NS). For patients with right sided pathways, the adjusted shortening of the atrial cycle length was 8 ± 32 ms for extrastimuli applied from the RV apex and 25 ± 23 ms from the summit of the septum (p = NS). The adjusted maximal shortening of the atrial cycle lengths were significantly different among the 3 groups (p = 0.0005 for the RV apex and p = 0.0001 for the summit of the septum). Again, further analysis revealed no significant difference between the posteroseptal and right-sided pathways. The difference in the adjusted shortening of the atrial cycle lengths obtained for all patients by VPCs applied at the RV apex and the summit of the RV septum was 14.5 ms (p = 0.006). This represents the difference in ventriculoatrial conduction times from VPCs induced at the summit of the RV septum and those induced at the RV apex.

Preexcitation index: The preexcitation index (Figure 7) for patients with left free wall pathways was 88 ± 21 ms when VPCs were applied from the RV apex and 86 ± 15 ms when they were applied from the summit of the RV septum (p = NS). In patients with posteroseptal and right free wall pathways, the preexcitation index was 52 ± 12 and 45 ± 13 ms from the RV apex and 41 ± 20 and 53 ± 8 ms from the summit of the RV septum, respectively (p = NS). The preexcitation indexes were significantly different among the 3 groups (p = 0.004 for the RV apex and p = 0.0001 for the summit of the septum). However, there was no significant difference in the preexcitation indexes between patients with posteroseptal and right free wall pathways. There was also no significant difference between the preexcitation indexes calculated from VPCs applied at the RV apex and those calculated from VPCs applied at the summit of the RV septum.

DISCUSSION

In this study, we compared stimulation of the RV apex versus the summit of the RV aspect of the septum in patients with orthodromic AV reentrant tachycardia.

Left free wall pathways: In our study, applying single VPCs from the RV apex during AV reentrant tachycardia in patients with left free wall pathways preexcited the atrium in only 13% of patients. Previous studies[1,3] have reported a 14 to 20% diagnostic yield when analyzing this technique in patients with left free wall pathways. In these studies, when VPCs were applied from the left ventricular free wall, a significant shortening of the atrial cycle length was noted in 95 to 100% of the patients. In a previously reported patient[1] with a left free wall pathway, a VPC induced in the RV outflow tract shortened the atrial cycle length more than a VPC induced from the RV apex. We therefore hypothesized that stimulation from the summit of the RV septum, which is closer to the reentrant circuit, would be more likely to advance the succeeding atrial electrogram. The addition of this technique did dramatically increase the incidence of a significant shortening of the atrial cycle length from 13 to 47%. Furthermore, when VPCs of all degrees of prematurity in which the sequence of retrograde atrial activation was unchanged from the sequence during tachycardia were considered, the diagnostic use of applying VPCs only from the RV apex was 67%, and increased to 93% when VPCs were applied from both the RV apex and summit of the septum. Shortening of the atrial cycle length was not observed in only 1 patient, probably related to his rapid tachycardia and the far left lateral location of his accessory pathway. The only other reported method that improves the diagnostic use of applying VPCs during tachycardia involving a left free wall accessory pathway is applying double ventricular extrastimuli from the RV apex.[2] This technique increased the diagnostic yield from 45 to 62%. Thus, inducing VPCs from both the RV apex and the summit of the RV septum, and recording the data for all degrees of prematurity where the atrial activation sequence is identical to that during tachycardia, is the diagnostically most useful RV stimulation technique available in patients with left free wall accessory pathways.

Several factors determine whether a particular VPC will gain entrance in the tachycardia circuit early enough to influence the next atrial activation, including the conduction time from the stimulation site to the tachycardia circuit, the rate of the tachycardia, and the refractoriness of the stimulated tissue. Given the excellent results obtained in previous studies[1,3] when extrastimuli were applied from the left ventricle, the poor performance of pacing from the RV apex is at least partially due to the time needed for transseptal activation. Weiss et al[8] compared ventriculoatrial conduction times in patients with accessory pathways during orthodromic AV reentrant tachycardia and using RV apical extrasystoles. In patients with left free wall pathways, the ventriculoatrial times increased a mean of 46 ms after RV extrasystoles, whereas in patients with septal pathways, the mean difference in ventriculoatrial times was 0 ms. The difference in ventriculoatrial times observed in patients with left free wall pathways is likely due to transseptal activation time. Similarly, Miles et al[7] found that in patients with left free wall pathways, an RV VPC had to be an average of 88 ms premature to first advance the succeeding atrial electrogram during tachycardia, whereas in patients with posteroseptal pathways,

the VPC only needed to be 38 ms premature. Our observations confirm these findings.

The improved diagnostic use of applying VPCs from the summit of the RV septum is likely due to being closer to the accessory pathway. The ventriculoatrial conduction time from extrasystoles applied at the summit of the septum was a mean of 14 ms shorter than when applied at the RV apex. Because of the 14 ms "head start," a greater number of patients will have a significant shortening of the atrial cycle length with an SH interval ≤35 ms when extrastimuli are applied at the summit of the RV septum than at the RV apex. Similarly, there is an increased probability of having a significant shortening of the atrial cycle length with any SH interval, before impinging on ventricular refractoriness.

Posteroseptal and right free wall pathways: In patients with left free wall pathways, the sequence of retrograde atrial activation is eccentric and, by itself, is diagnostic of the presence of an accessory pathway. However, in patients with posteroseptal pathways, the sequence of retrograde atrial activation during tachycardia may be consistent with normal retrograde AV nodal conduction[9] and bundle branch block may not have a significant effect on the ventriculoatrial conduction times. Furthermore, patients with atypical AV junctional reentrant tachycardias may have a similar atrial activation sequence during tachycardia.[10] In patients with posteroseptal accessory pathways, a VPC applied during tachycardia to the summit of the RV septum while the His bundle was refractory advanced the next atrial depolarization in all patients. If VPCs were applied only from the RV apex, atrial preexcitation would not have been achieved in 2 of the 5 patients.

Because of the observed overlap in the adjusted shortening of the atrial cycle lengths and preexcitation indexes for all accessory pathway locations (Figure 7), these parameters cannot totally differentiate these 3 types of accessory pathways. However, a VPC applied at the summit of the RV septum on or after the inscription of the His potential is most likely to shorten the atrial cycle length in a patient with a posteroseptal pathway and unlikely to affect the atrial cycle length in a patient with a left free wall pathway (not observed in any of our patients with stimulation from either RV site).

Study limitations: Stimulation of the summit of the RV septum needs meticulous attention to technical details. This technique cannot be used when the summit of the septum cannot be paced without simultaneous capture of the low septal right atrium. When stimulating from the summit of the septum, it is critical to ensure that the sequence of retrograde atrial activation remains unchanged and that there is ventricular capture (Figure 1).

Summary and clinical implications: In summary, we found that stimulation from the summit of the RV septum markedly enhances proof of left sided accessory pathway participation in the tachycardia compared with stimulation from the RV apex. Although the presence of a left-sided accessory pathway can be established by various means, proof that it participates in the tachycardia circuit is more difficult to attain. We have found that RV stimulation from both the apex and the summit of the septum establishes strong evidence of participation of a left free wall accessory pathway and does so better than any previously suggested RV stimulation techniques. Although stimulation from the summit of the RV septum cannot localize an accessory pathway with the precision needed for catheter ablation, this technique may also be critical in identifying the presence of an accessory pathway and its approximate location during limited electrophysiologic studies if recordings of left atrial activity are not obtained (i.e., difficulty in cannulating the coronary sinus). Finally, distinguishing orthodromic AV reentrant tachycardia using a posteroseptal accessory pathway from atypical AV nodal reentrant tachycardia may be difficult, because they both have similar atrial activation sequences and may have similar ventriculoatrial conduction times. Only stimulation from the summit of the RV septum resulted in shortening of the atrial cycle length in all patients with posteroseptal accessory pathways, making it a useful technique to differentiate these tachycardias from atypical AV nodal reentrant tachycardia.

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Silent Myocardial Ischemia in Men With Systemic Hypertension and Without Clinical Evidence of Coronary Artery Disease

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The prevalence, characteristics and circadian pattern of silent myocardial ischemia, and its association with ventricular arrhythmias was studied in hypertensive men aged 35 to 70 years (mean 61) without clinical cardiac disease. Participants were withdrawn from diuretic treatment and received 1 month of oral electrolyte repletion with 40 mmol of potassium chloride, and 400 mg of magnesium oxide daily. Twenty-four-hour Holter monitoring was then performed. Episodes of silent myocardial ischemia occurred in 50 of 186 men (27%) and lasted from 2 to 289 minutes (mean 30 and median 18). Statistical analysis comparing the interval from midnight to 6 A.M. with each of the other three 6-hour time intervals revealed that participants were less likely to have silent myocardial ischemia in this period (p <0.01 for each comparison) than at other times of the day. There was little difference in the proportion of men with a frequent or complex ventricular arrhythmia during the entire day or within 1 hour of the silent myocardial ischemic episode (or during a comparable time period) comparing those with to those without silent myocardial ischemia. These findings indicate that silent myocardial ischemia occurs in approximately 25% of an older population of hypertensive men without history of symptomatic cardiac disease. The circadian pattern of frequency of silent ischemic events in men free of clinical cardiac disease is similar to that reported for patients with cardiac disease and coincides with that reported for sudden death. There was no significant association between silent myocardial ischemia and ventricular arrhythmias.

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Transient myocardial ischemia in the absence of angina or other cardiac symptoms has been labeled silent myocardial ischemia and is usually observed in patients with demonstrated coronary artery disease (CAD).[1-4] Myocardial ischemia, whether silent or symptomatic, is associated with changes in myocardial perfusion, wall motion abnormalities and hemodynamic evidence of myocardial impairment.[2,5] It is also associated with an increased risk of death for several categories of CAD patients including those after myocardial infarction and with unstable angina.[6-8] Less is known about the prevalence of silent myocardial ischemia in patients with risk factors for CAD but without clinical cardiac disease, even though these persons are also at increased risk for cardiac death. Furthermore, the role of silent myocardial ischemia in the development of lethal ventricular arrhythmias is not known, although studies have shown that the presence of ventricular arrhythmias on resting electrocardiogram or 24-hour Holter monitoring is associated with a significant increase in mortality, even in patients with no history of angina or myocardial infarction.[9,10] If silent myocardial ischemia is associated with ventricular arrhythmias in asymptomatic but high-risk patients, intervention studies designed to evaluate the benefit of reversing silent myocardial ischemia with the aim of decreasing ventricular arrhythmias and thus presumably the risk of cardiac death would be indicated. We evaluated silent myocardial ischemia on 24-hour ambulatory Holter monitoring in hypertensive men who had been withdrawn from diuretic therapy, and repleted with oral potassium and magnesium for 1 month. Men with a history of angina or myocardial infarction were eliminated from analysis. This study design enabled us to evaluate the prevalence and pattern of silent myocardial ischemia, and its association with ventricular arrhythmias, in an asymptomatic population of hypertensive men free of electrolyte abnormalities and clinical cardiac disease.

METHODS

Study sample and design overview: Details of the study design and participant selection process were previously presented.[11] Briefly, the Hypertension Arrhythmia Reduction Trial is a clinical trial designed to assess the frequency and severity of ventricular arrhythmias associated with the use of various diuretic combinations. Hypertensive men aged 35 to 70 years with resting electrocardiographic abnormalities were selected as study subjects, because the Multiple Risk Factor Intervention Trial suggested that they may be especially at risk for

sudden death with diuretic use.[12] The portion of the study described in this report was performed after diuretic withdrawal and electrolyte repletion (see later). The study group was recruited both from clinical populations and by a direct mail campaign. Subjects were included in the study if they were receiving diuretics for ≥6 months and had a diastolic blood pressure <95 mm Hg, or if they were not receiving diuretic therapy, but had history of hypertension and were either receiving nondiuretic antihypertensive drugs or had a diastolic blood pressure ≥90 but <105 mm Hg.

We excluded men who were receiving medications that may influence the development of ventricular arrhythmias, such as antiarrhythmic drugs, β blockers, theophylline and digitalis preparations, phenothiazines and tricyclic antidepressants. We also excluded men with history of myocardial infarction, congestive heart failure, angina pectoris, renal insufficiency (creatinine >2 mg/dl) or other serious illness (including psychiatric disability), or inability or unwillingness to give informed consent. Men with electrocardiographic findings (left ventricular hypertrophy and left bundle branch block) that would make interpretation of silent myocardial ischemia on Holter recordings difficult were also excluded.

Subjects were withdrawn from diuretic treatment and received 1 month of oral electrolyte repletion with both 40 mmol of potassium chloride and 400 mg of magnesium oxide (containing 241 mg of elemental magnesium) daily. Serum potassium and magnesium were then measured, and a continuous 24-hour Holter monitoring test was performed.

Continuous Holter monitoring: Continuous 24-hour Holter monitoring was performed using the Cardiotechorder III dual lead system with a frequency response of 0.5 to 100 Hz, thereby meeting the American Heart Association's specifications for heart rate and ST-segment changes.[13] The electrocardiogram was recorded continuously on tape using a cassette system. The 2 lead systems used were V_5 and V_1. Patient electrodes were selected to minimize patient discomfort, noise, skin-electrode impedance, polarization or other malfunction.

Tapes were sent to Cardio Data Systems (Haddonfield, New Jersey) for analysis. Whole tapes were printed at high speed on recording paper using the Cardio Data Corporation Mark IV Holter Analyzer. Specific areas of interest were printed at real time and evaluated by an analyst. Abnormal ST-segment changes were defined as ≥1 mm of ST-segment depression occurring 80 ms after the J point, lasting for ≥1 minute and separated from other episodes by ≥1 minute. The onset and end of each episode was measured at the point of first deviation from the baseline.

For arrhythmia analysis, specific areas of interest (identified by irregularity in the QRS pattern) were printed at real time and evaluated by an analyst. Ventricular arrhythmias were classified (in a manner similar to that of Lown et al)[14] according to the presence of the following arrhythmia types: ventricular premature complexes, multiform extrasystoles, ventricular couplets, ventricular tachycardia, and R-wave on T-wave

ventricular premature complexes. We created a summary category of the presence of a frequent (≥30 ventricular premature complexes/hour) or complex (presence in 24 hours of any of the following: multiform extrasystoles, ventricular couplets or tachycardia, or R-wave on T-wave ventricular premature complexes) ventricular arrhythmia for ≥1 of 24 hours. The precision of these measurements is indicated by their within-individual correlation of ventricular arrhythmias on continuous 24-hour Holter monitoring before and after diuretic treatment; kappa coefficients for the whole cohort were 0.74 (95% confidence interval 0.61, 0.88) for the presence of ≥30 ventricular premature complexes/hour, and 0.47 (95% confidence interval 0.33, 0.60) for the presence of a frequent or complex ventricular arrhythmia.

Statistical analysis: Silent myocardial ischemia, ventricular arrhythmias and mean heart rate were recorded per hour for a 24-hour period. To determine if silent ischemic episodes were associated with the occurrence of ventricular arrhythmias, we compared the frequency of ventricular arrhythmias that occurred in a 3-hour time span surrounding the silent ischemic event with that of a randomly assigned, frequency-matched (by diurnal distribution of silent ischemia) 3-hour time period in control subjects without silent ischemia. Proportions of participants with a complex or frequent ventricular arrhythmia in the 1 hour before the silent ischemic event, in the 1 hour after the event and in a 3-hour time span (including the hour of the event) were compared between those with and without silent myocardial ischemia using chi-square tests of homogeneity.

The proportion of participants with silent myocardial ischemia in ≥1 hour of each 6-hour time block (6 A.M. to noon, noon to 6 P.M., 6 P.M. to midnight, and midnight to 6 A.M.) was determined. The analysis comparing the risk of having silent myocardial ischemia at a given time of day to that at midnight to 6 A.M. was performed using a method that takes into account the within-person correlation among outcomes (silent ischemic episodes over time) for each participant. This approach (based on generalized linear models) regards the correlation among multiple observations in the same subject as a "nuisance" parameter.[15] We used a logit function to estimate regression coefficients and standard errors, and an exchangeable correlation matrix that assumes correlations, which represent the weighted average correlation among observed outcomes, are similar over time.[16] Associations are presented as odds ratios with 95% confidence intervals. Statistical analysis was performed using Statistical Analysis System software on an IBM 4341 mainframe computer.

RESULTS

Study sample: The demographic and clinical characteristics of the study participants are listed in Table I. The study sample included 186 men, of whom 50 (27%) had episodes of silent myocardial ischemia. There was no difference in age between men with and without silent ischemia (mean 61 years in both groups). Mean serum potassium was 4.3 mEq/liter, and mean serum magnesium was 2 mEq/liter in participants both with and without silent ischemia, indicating successful reple-

TABLE I Characteristics of Study Sample Comparing Participants With and Without Silent Myocardial Ischemia

	Silent Myocardial Ischemia	
Characteristic	Present	Absent
Number	50	136
Age (yr)*	61 (9)	61 (8)
Race (%)		
Asian	6	6
Black	6	15
Hispanic	4	5
Indian	0	1
White	84	72
Other	0	2
Weight (lbs)*	181 (27)	192.3 (33)†
Body mass index*	27 (3)	28 (4)†
Systolic BP (mm Hg)*	144 (15)	145 (18)
Diastolic BP (mm Hg)*	85 (10)	88 (10)
Body surface area (m²)*	1.9 (0.2)	1.9 (0.2)
Serum potassium*	4.3 (0.3)	4.3 (0.4)
Serum magnesium*	2.0 (0.2)	2.0 (0.2)
Alcohol (current, %)	72	66
Smoke (%)		
Current	18	18
Past	60	54
Never	22	27
Antihypertensive other than diuretic (%)	30	34

*Mean (SD).
†p <0.05.
BP = blood pressure.

TABLE II Distribution of Ventricular Arrhythmias in Participants With and Without Silent Myocardial Ischemia

	Silent Myocardial Ischemia		
	Present	Absent	p Value
Number	50	136	
Any complex or frequent ventricular arrhythmia (%)*	46	48	0.82
Complex or frequent ventricular arrhythmia (%)			
Within ± 1 hour of event	31	24	0.29
Within 1 hour after event	21	17	0.54
Within 1 hour before event	21	15	0.39

*Complex or frequent ventricular arrhythmia defined as presence of any of the following: ≥30 ventricular premature complexes/hour, or any of the following grades: multiform extrasystole, ventricular couplet or ventricular tachycardia.

tion of these electrolytes. In terms of other characteristics, there was little difference between men with or without silent myocardial ischemia, except that those without silent myocardial ischemia were heavier and had a greater body mass index (p <0.05).

Echocardiograms were obtained (data not shown). There was no difference in the proportion of men with silent myocardial ischemia, between those who met echocardiographic criteria for left ventricular hypertrophy (left ventricular mass index >134 g/m²) and those who did not.

Pattern of silent myocardial ischemic episodes: There were 74 episodes of ischemia in 50 participants (range 1 to 4 per participant); most participants (64%) who had silent myocardial ischemia had only 1 episode in 24 hours (data not shown). Silent myocardial ischemic episodes lasted from 2 to 289 minutes (mean 30);
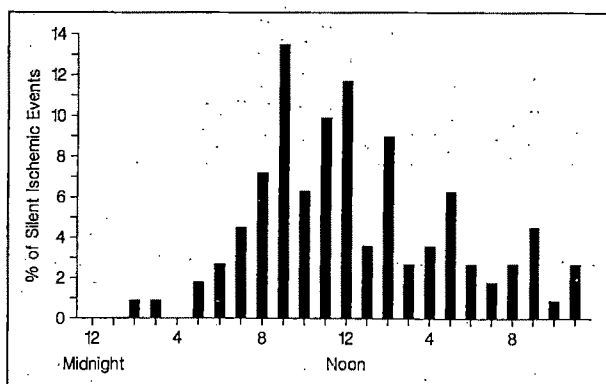
FIGURE 1. Distribution of silent myocardial ischemic episodes by time of day.

25% of events lasted from 2 to 10 minutes, 50% were ≤18 minutes, and 75% were ≤38 minutes.

Figure 1 presents the hour-by-hour frequency of silent myocardial ischemic episodes. There was a consistent pattern of less silent myocardial ischemic episodes between midnight and 6 A.M. than during other times of the day. Statistical analysis comparing each of the other three 6-hour time intervals with that from midnight to 6 A.M. revealed that participants were less likely to have silent myocardial ischemia in this period (p <0.01) than at other times of day.

Silent myocardial ischemia and ventricular arrhythmias: There was little difference in the proportion of participants with a frequent or complex ventricular arrhythmia on 24-hour Holter monitoring between those with (46%) and without (48%) silent myocardial ischemia (Table II). The proportion of men with a frequent or complex ventricular arrhythmia within 1 hour of the silent myocardial ischemic event was somewhat increased compared with that of a similar time period in participants without silent myocardial ischemia, but the differences were not statistically significant.

DISCUSSION

Most prior studies of silent myocardial ischemia included large proportions of participants with various cardiac disorders.[1-4,6-8,17] In our study, men with history of angina or myocardial infarction, as well as those with electrocardiographic left ventricular hypertrophy, were eliminated from analysis, and all participants were repleted with potassium and magnesium. This enabled us to study men without clinical cardiac disease, and to avoid the potential effects of deficiencies in potassium and magnesium on silent myocardial ischemia and ventricular arrhythmias.

In our study, 27% of men had episodes of silent myocardial ischemia. This is a much higher proportion of participants with silent myocardial ischemia than that noted by Selwyn et al[18] in a study of healthy normal subjects, where only 2 of 100 participants had horizontal ST-segment depression on 24-hour Holter monitoring. Their population included younger men and women (age range 20 to 50 years) without hypertension. Similar findings to those of Selwyn were noted in another

study of healthy younger men and women.[19] In another study, 11 of 17 asymptomatic men who had ischemic-type ST-segment depression (≥2 mm) during treadmill exercise testing were found to have silent myocardial ischemia.[20] Participants were older (mean age 62 years), and all but 1 had single or multiple cardiac risk factors, in addition to being men. All 11 participants with silent myocardial ischemia had significant CAD (≥50% stenosis) on angiography. These findings suggest that cardiac risk factors are associated with silent myocardial ischemia and that the presence of silent myocardial ischemia identifies a group of subjects at risk for CAD. Considerable day-to-day variability has been noted in the frequency of silent ischemic events in patients with CAD as recorded by Holter monitoring.[21] Thus, our finding of 27% represents the minimum proportion of patients in our study with silent myocardial ischemia.

Myocardial infarction and sudden death do not occur randomly throughout the day, but rather in a circadian pattern with an increased frequency in the morning.[22,23] Several physiologic processes such as heart rate, coronary blood flow, systemic pressure, platelet aggregability, plasma cortisol, tissue-type plasminogen activity and plasma epinephrine have a similar pattern.[23] We previously reported that ventricular arrhythmias become more prevalent when subjects go from sleep to awakening.[24] We now note that there is a similar circadian variation in silent myocardial ischemia. This pattern of silent myocardial ischemia was previously reported in men with clinical cardiac disease.[3,25,26] Our results extend these findings to men with hypertension but without symptomatic cardiac disease; they are of interest because many episodes of sudden death occur as the initial manifestation of cardiac disease.[27]

Most studies have been unable to document a strong association between silent myocardial ischemia and ventricular arrhythmias.[28] However, 1 study of 15 patients who survived out-of-hospital ventricular fibrillation found that 12 had exercise-induced silent myocardial ischemia in the absence of angina.[29] Another study found that ventricular arrhythmias were associated with 18% of silent myocardial ischemic episodes in patients with unstable angina.[17] However, in this study there was no comparison with the frequency of ventricular arrhythmias during a similar time period in comparable patients without silent myocardial ischemia. In another recent report, ventricular arrhythmias were associated with ischemic episodes in 10 of 97 participants.[26] Again, there was no comparison with the frequency of ventricular arrhythmias during a similar time period in comparable patients without silent myocardial ischemia. We were unable to demonstrate a statistically significant difference in the proportion of participants with ventricular arrhythmias between those with and without silent ischemia. However, our study lacks the power to detect small differences in ventricular arrhythmias between the 2 groups. If, as our study suggests, there is a 20% increase between the proportion of participants with a frequent or complex ventricular arrhythmia within 1 hour, either before or after the silent myocardial isch-

emic episode, compared with that of a similar time period in participants without silent myocardial ischemia, a sample size of approximately 1,900 would be needed to detect such a small increased risk (based on a 2-sided significance level of 0.05, and a power of 80%, and assuming that 25% of participants had silent ischemic episodes).

Silent myocardial ischemia has been associated with a poor prognosis in patients with unstable angina and after infarction.[6-8] Some investigators have suggested that patients with silent myocardial ischemia should be treated in the same manner as those with classic angina.[30] Whether a similar prognosis is predicted by silent myocardial ischemia in patients without clinical cardiac disease but with cardiac risk factors and whether these patients would benefit from medical or surgical intervention needs further study.

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Effects of Combined Hydrochlorothiazide and Amiloride Versus Single Drug on Changes in Salt Taste and Intake

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Hydrochlorothiazide stimulates salt intake without altering salivary or gustatory function. Amiloride reportedly reduces salivary sodium levels and salt taste. It was hypothesized that these unintended drug actions would be attenuated by concurrent use of these 2 diuretics. Normotensive adults (n = 23) were administered placebo for 2 weeks, active combination drug Moduretic® for 4 weeks, and placebo again for 2 weeks in a double-blind protocol. Salivary flow, gustatory function and sodium intake were monitored at the end of each period, together with selected physiologic measures (i.e., plasma aldosterone, plasma renin activity, body composition, blood pressure and heart rate). No significant changes were observed for salivary flow, salt taste or sodium intake. These findings indicate that amiloride and hydrochlorothiazide used in combination can reduce drug effects that may compromise the efficacy of either drug when used alone.

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The blood pressure-lowering property of diuretics is influenced by the concurrent level of salt use. Thiazide diuretics elicit a marked (28 to 64%) but unconscious increase in salt intake.[1–5] This level of additional intake is sufficient to compromise the therapeutic efficacy of the agent. No mechanism underlying the shift in intake has been elucidated. One possibility relates to the potassium wasting associated with thiazides, because amiloride, a potassium-sparing diuretic, does not elicit an increase in salt intake.[5] The primary aim of the present study was to test this hypothesis in adult humans by preventing potassium loss in thiazide-treated subjects through concurrent administration of amiloride. The effects of blocking potassium loss on salt taste were also assessed, because this could be related to intake.

METHODS

Study protocol: The protocol previously used to demonstrate the effects of hydrochlorothiazide or amiloride alone on salt taste and intake was followed for this study using the combination drug.[5,6] The dosage of hydrochlorothiazide and amiloride used separately by subjects in the prior study was identical to that of the combination drug used in this study. Baseline characteristics of participants in the prior and current studies are presented in Table I as evidence that subjects were comparable in relevant attributes (e.g., blood pressure, body weight, age and gender distribution). In both studies, volunteer subjects were recruited by public advertisement and received modest payment. Participants used no medication and, based on responses to a questionnaire containing distracting items to mask the intent of the study, did not purposefully restrict salt use. Each subject had a normal physical exam and appropriate clinical laboratory tests. All subjects signed an informed consent form. All research procedures were approved by the Committee on Studies Involving Human Beings of the University of Pennsylvania.

For the present study, identical tablets containing either active drug (amiloride [5 mg] and hydrochlorothiazide [50 mg] [Moduretic®]) or placebo were provided by Merck, Sharp and Dohme. During the 8 weeks after entry into the study, subjects were periodically provided with vials of pills and instructed to take 1 each morning with breakfast. During weeks 1 to 2 (baseline period) and 7 to 8 (follow-up period), the vials contained placebo tablets, and during weeks 3 to 6 (active drug period), they contained Moduretic. Subjects and research personnel administering all tests were unaware of the contents of the vials. Pill counts at weeks 1, 2, 4, 6 and 8 were used to assess compliance.

TABLE I Mean Selected Physiologic Measures of 24 Subjects Treated with Hydrochlorothiazide (50 mg/day), 24 Treated with Amiloride (5 mg/day) in a Prior Study,[11] and 23 at Baseline (end of week 2), After Four Weeks of Active Diuretic Treatment and After Two Additional Weeks of Placebo

| | Historic Data | | Current Data HCTZ + Amiloride | | |
	HCTZ	Amiloride	Baseline	Active	Follow-Up
No. of subjects	24	24	23		
Sex (M/F)	9/15	11/13	7/16		
Age (yr)	27 ± 8	31 ± 6	24 ± 5		
Body weight (kg)	67.3 ± 8.3	66.8 ± 6.4	64.9 ± 12.8	63.6 ± 12.4*	64.7 ± 11.7
Blood pressure (mm Hg)					
Systolic	110 ± 8	106 ± 8	112 ± 12	110 ± 12	109 ± 12
Diastolic	71 ± 8	69 ± 8	66 ± 8	66 ± 8	65 ± 7
Body composition					
Lean (%)			76 ± 7	75 ± 5	76 ± 7
Fat (%)			24 ± 7	25 ± 6	24 ± 7
Water (%)			56 ± 6	55 ± 6†	56 ± 6
Heart rate (beats/min)			71 ± 9	73 ± 13	69 ± 7

*p <0.05 versus baseline and follow-up; †p <0.05 versus follow-up.
HCTZ = Hydrochlorothiazide.

Subjects participated in a battery of tests and procedures that were performed 3 times during the study (second week of baseline, fourth week of drug use, and final week of follow-up). Subjects kept a 7-day diet record during each of these weeks, and used preweighed salt and pepper shakers for cooking and table use of these condiments. Subjects also collected four 24-hour urine samples on the last 4 days of the 3 study periods. Finally, a blood sample was collected, taste testing was conducted, and weight, blood pressure, pulse and body composition were measured on the final day of each period.

Urinalysis: Subjects collected urine in 2-liter, widemouthed, plastic containers containing 2 g of boric acid (a preservative). Samples were stored in a cool place and returned to the laboratory in <3 days. All samples were analyzed for total volume, sodium and potassium by flame photometry, and for creatinine colorimetrically (Sigma diagnostic kit-555). Creatinine was measured as an index of the completeness of urine collection. Samples were also assayed for plasma renin activity and aldosterone concentration by radioimmunoassay as indexes of diuretic activity.

Dietary analysis: Subjects were trained to keep diet records, using food models and printed materials to provide estimates of portion size. Information was recorded concerning the type of food ingested, how it was prepared, and portion size. Records were analyzed by 1 clinician using version 5.0 of the Nutritionist III nutrient database (N-Squared Computing, Salem, Oregon). Sodium derived from discretionary sources (table and cooking) was determined by the use of preweighed shakers containing salt "marked" with lithium carbonate.[7] Lithium was added at a concentration where the highest expected intake would correspond to only 1% of a therapeutic dose and thus would not exert any measurable influence on taste or vasopressin levels. Subjects were instructed to use the shakers in their customary fashion during the first 3 days of urine collections. By monitoring urinary lithium excretion, it was possible to ascertain the quantity of salt missing from the shaker that was actually consumed. The urinary concentration of lithium was determined by flame photometry. Preweighed pepper shakers were also provided to determine whether there was any global change in seasoning habits over the study and to mask the true purpose of providing the salt shaker. Except for weeks 5 and 7, dietary and health information was obtained weekly by questionnaire.

Body composition: Lean body mass, and body water and fat were determined in recumbent subjects by bioelectrical impedance analysis (model 101, RJL Systems, Detroit, Michigan) to assess the effect of the diuretic on fluid balance. Subjects were weighed in light, indoor clothing on a balance scale.

Taste tests: Taste recognition thresholds, perceived intensity ratings and hedonics were determined for salty, sweet and sour solutions by previously reported procedures.[6] Thresholds were determined by a staircase procedure. Whereas samples representing the 3 qualities were intermixed, a total of 7 trials were presented for each quality. Samples (10 ml) were presented in increasing or decreasing concentrations until correct or incorrect identifications were obtained, respectively. The geometric mean of the last 6 trial inflection points was the estimate of threshold sensitivity. Stimuli included salt ($0.8 - 1.0 \times 10^{-5}$ M), sucrose ($0.8 - 1.0 \times 10^{-5}$ M) and citric acid ($0.01 - 1.5 \times 10^{-7}$ M) prepared as serial half-dilutions. Sweet and sour stimuli were included to allow determination of the specificity of noted changes in salt taste. The 5 highest concentrations were used for intensity and hedonic judgments. Intensity was determined in duplicate as the mean of numeric ratings that subjects assigned to each sample's strength of sensation. Hedonic ratings were obtained in duplicate, with 9-point category scales labeled from "like extremely" to "dislike extremely."

Saliva collection: Resting and stimulated saliva were collected according to the method of Navazesh and Christensen.[8] Salivary flow was stimulated by having

TABLE II Mean Urinary and Plasma Values of 23 Subjects at Baseline (end of week 2), After Four Weeks of Active Diuretic Treatment and After Two Additional Weeks of Placebo

	Baseline	Active	Follow-Up
Creatinine (g/24 hours)	1.27 ± 0.49	1.20 ± 0.51	1.16 ± 0.56
Urine volume (ml)	1226 ± 589	1396 ± 636	1255 ± 600
Urinary lithium	0.54 ± 0.16	0.65 ± 0.19*	0.36 ± 0.10
Aldosterone (μg/24 hours)	10.34 ± 9.45†	30.11 ± 17.39	7.19 ± 3.56†
Plasma renin activity (N/ml/hour)	4.15 ± 5.13†	7.98 ± 4.03	2.91 ± 2.31†
Serum sodium (mM/L)	139.6 ± 2.5	139.2 ± 1.4	140.2 ± 2.3
Serum potassium (mM/L)	4.15 ± 0.54	4.04 ± 0.42	4.22 ± 0.39

*$p < 0.05$ versus follow-up; †$p < 0.01$ versus active treatment.

subjects chew an unflavored gum base at a rate of 80 chews/min. Flow rate was determined by dividing total volume collected by collection time.

Statistical analyses: The protocol used a within-subject design, where all participants were tested during baseline, active diuretic treatment, and again after 2 weeks of placebo administration. If the proportion of within-subject variance accounted for by the treatment conditions was only 0.3, a sample of 23 would allow a treatment effect greater than this to be found significant at the 5% probability level with 85% power.

Repeated measures analysis of variance was used to assess treatment effects. When significant treatment effects were observed, the Tukey test was used for posthoc comparisons. Associations between measures were evaluated by Pearson correlation coefficients. A p level of 0.05 was used as the criterion for statistical significance. Analyses were conducted using Statisical Package for the Social Sciences/PC+ (version 4.0) software.[9]

RESULTS

Sodium intake and excretion: Urinary and hematologic data pertinent to the assessment of sodium intake are listed in Table II. Only 11 urine samples (4%) were excluded from analyses owing to creatinine values below the pre-established minimal criterion of 0.6 g/24 hours. Urinary creatinine and volume were stable throughout the study. Urinary aldosterone was significantly ($F[2,30] = 13.73$; $p < 0.001$) increased during ac-

tive treatment, as was plasma renin activity ($F[2,38] = 10.03$; $p < 0.001$). Pill counts revealed that the mean number of doses missed was 1.9 of 28 during the active treatment period. Serum sodium values were not significantly changed during the study.

Urinary sodium excretion and values of sodium intake based on diet records are presented in Figure 1. Although values for both intake measures increased during the active drug period, the changes were not statistically significant. Urinary sodium excretion correlated significantly with estimated dietary intake at baseline ($r = 0.47$, $p < 0.05$), active treatment ($r = 0.67$, $p < 0.001$) and follow-up ($r = 0.67$, $p < 0.001$).

Discretionary salt use was significantly increased during the active treatment period compared with follow-up ($p < 0.02$) and tended to be higher than at baseline, but this difference was not significant (Figure 2). Pepper use showed a similar pattern, but the changes were not statistically significant. Urinary lithium excretion (an index of discretionary salt use) was significantly higher during the active period than at follow-up ($p < 0.01$). However, determination of the recovery revealed that only a mean of 17% of the sodium missing from the shakers was actually ingested (approximately 8 mEq/24 hours). Discretionary salt contributed only approximately 5% to total salt intake. Food cravings beginning subsequent to the initiation of active drug treatment were reported by 5 subjects; 3 were directed toward sweet items, and 2 toward salty foods.
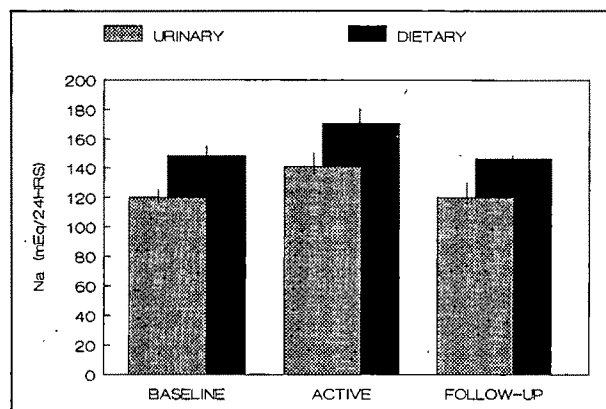
FIGURE 1. Mean urinary and dietary estimates of sodium (Na) intake at baseline (end of week 2), after 4 weeks of active diuretic treatment (ACTIVE) and after 2 additional weeks of placebo use (FOLLOW-UP).
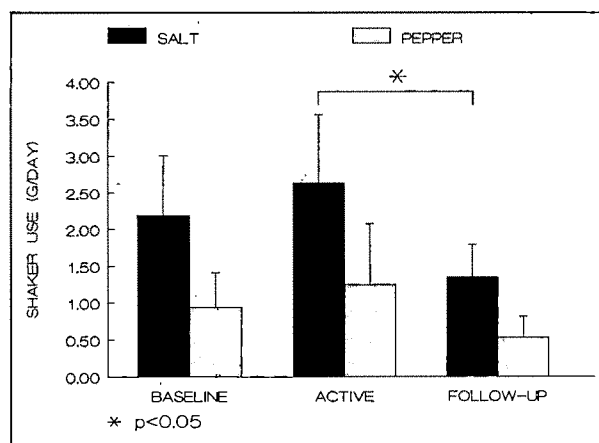
FIGURE 2. Mean discretionary (table and cooking) salt and pepper use from preweighed shakers at baseline (week 2), after 4 weeks of diuretic treatment (ACTIVE) and after 2 additional weeks of placebo use (FOLLOW-UP).

	Baseline	Active	Follow-Up
Threshold (M)			
Salt	20.6 ± 9.8	14.0 ± 3.6	15.1 ± 2.8
Sucrose	19.0 ± 5.7	12.5 ± 4.8	10.8 ± 2.2
Citric acid	12.2 ± 2.2	8.62 ± 1.2	14.1 ± 5.0
Subjective range			
Salt	0.58 ± 0.39	0.63 ± 0.24	0.94 ± 1.28
Sucrose	0.94 ± 2.08	1.36 ± 3.27	0.63 ± 0.54
Citric acid	0.96 ± 0.75	0.75 ± 0.37	0.71 ± 0.28
Rating for preferred conc.			
Salt	5.39 = 0.87	5.54 ± 1.10	5.77 ± 1.06
Sucrose	4.27 ± 2.09	5.00 ± 2.58	4.84 ± 2.15
Citric acid	6.60 ± 1.49	6.75 ± 1.32	6.62 ± 1.22
Salivary flow (g/min)			
Resting	0.54 ± 0.05	0.63 ± 0.08	0.61 ± 0.07
Stimulated	0.90 ± 0.10	0.98 ± 0.12	1.17 ± 0.16

Conc. = concentration; M = molarity.

Potassium intake and excretion: No significant changes in either reported dietary potassium ingestion or urinary potassium excretion were observed (Figure 3). Correlations between the measures were statistically significant during each study period (baseline: r = 0.75, p <0.001; active treatment: r = 0.75, p <0.001; and follow-up: r = 0.58, p <0.005). Serum potassium was not significantly changed during the study (Table II).

Gustatory and salivary findings: No significant differences in salt, sucrose or citric acid recognition thresholds, perceived intensity ratings or taste preference were observed (Table III). Salt thresholds tended to decrease during treatment compared with baseline, but similar trends were observed for the other taste qualities, and values did not rebound consistently during follow-up. Resting and stimulated salivary flow rates were not significantly altered by treatment (Table III).

Physiologic and biochemical indexes: The diuretic did not significantly alter heart rate or blood pressure in these normotensive subjects (Table I). Body weight decreased significantly by 1.3 kg ($F[2,40] = 3.79$; $p < 0.05$) during diuretic treatment. This was attributable

FIGURE 3. Mean urinary and dietary estimates of potassium (K) intake at baseline (week 2), after 4 weeks of diuretic treatment (ACTIVE) and after 2 additional weeks of placebo use (FOLLOW-UP).

to a reduction of fat-free weight ($F[2,38] = 8.69$; $p = 0.001$) and, more specifically, body water ($F[2,38] = 5.79$; $p = 0.006$). Post-hoc tests indicated the reduction in body water during diuretic treatment was significant compared with follow-up ($p < 0.05$), and nearly so compared with baseline ($p < 0.06$).

DISCUSSION

Evidence that potassium wasting may promote salt intake derives from data that (1) thiazides[10] and furosemide[11,12] (potassium-wasting diuretics) elicit a marked salt appetite in rats, (2) dietary potassium depletion leads to an increased preference for and intake of salt in rats,[13–15] (3) salt appetite is positively associated with the urinary potassium/sodium ratio in pharmacologic studies with rats,[11,16] (4) thiazides stimulate salt intake in humans,[1–5] and (5) salt craving occurs in some patients with Bartter's disease.[17] In contrast, amiloride (a potassium-sparing agent) has not been associated with increased sodium intake in humans.[5] Thus, by reducing potassium loss, it was hypothesized that co-administration of amiloride with hydrochlorothiazide would ameliorate the effects that thiazide alone would have on salt intake. The present data support this hypothesis. Although this conclusion is based on contrasting effects noted in historic controls, the criteria for participant recruitment, and the protocol used in earlier studies were identical to the conditions of this work.

Specifically, we demonstrated in 2 independent studies that hydrochlorothiazide alone at a dose of 50 mg/24 hours (as in this study) leads to an unwitting 30 to 50% increase in sodium intake.[5] Amiloride alone (at the same dose used in this study) did not elicit this effect, despite a comparable level of diuresis. In the present study, there was a small tendency (indicated by both urinary excretion and diet records) for sodium intake to increase during combined drug administration (16 to 18%), but this effect was not statistically significant. There was only a small and nonsignificant trend for increased discretionary salt use.

The present data do not permit a determination of whether the observed reduction of thiazide-stimulated sodium intake is specific to amiloride, or may be generalized to other potassium-sparing diuretics such as triamterene and spironolactone, or to the maintenance of potassium balance with potassium salts. The mechanistic role of potassium balance can be further demonstrated by the more direct approach of administering potassium to subjects treated with a thiazide diuretic and by testing with other potassium-sparing agents.

We previously observed decreased salt taste recognition thresholds in amiloride-treated subjects.[6] This effect was not observed with hydrochlorothiazide. In the present study, the combination of these agents did not lead to a significant change in taste function. This may be due to an antagonistic action between the agents that influences whatever mechanism accounted for the amiloride-related shift in salt taste noted previously. Alternatively, the decreased taste threshold reported earlier may have been a chance event. Owing to the potential importance of this observation with respect to the development of salt substitutes, we have attempted to repli-

cate and better characterize the amiloride-mediated decrease in salt taste threshold in normotensive and hypertensive subjects. However, this additional (unpublished) work has not confirmed the earlier reported change in salt taste.
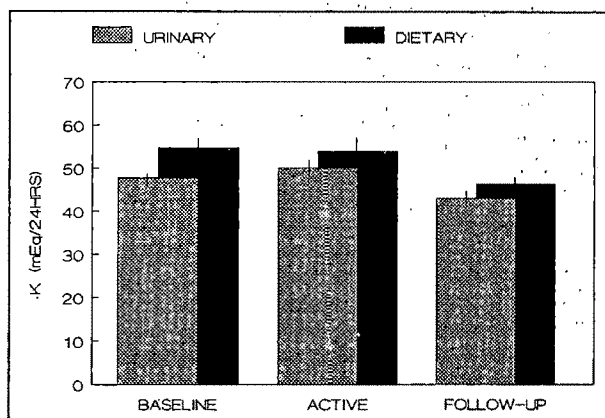
Salivary flow was monitored because of its potential influence on taste. Although there are reports of xerostomia in diuretic users,[18] the present findings support the preponderance of data in the literature, which indicate that such effects are uncommon.[6,19,20] It should be noted that the relation between salivary flow and subjective reporting of "dry mouth" is not strong,[21] and that reductions in resting flow of 40 to 50% are generally needed to elicit comments of dryness.[22] The explanation for these discrepant observations is unclear, but may relate to drug-induced shifts in salivary composition[23] or marked individual variation in sensitivity to small changes in flow.

Finally, it is important to note that discretionary sources of sodium were minor contributors to total intake in our normotensive subjects who were screened to ensure that they did not purposefully restrict salt use. The point may be more relevant among hypertensive patients with an incentive to limit sodium intake. This observation is consistent with a growing literature[24] that suggests that efforts to moderate sodium intake by the traditional approach of restricting discretionary sources may not be successful.[25] Maximizing the efficacy of diuretic therapy by moderating sodium intake needs greater control over the use of highly processed foods that are the principle sources of sodium in the diet.[24] Our data on discretionary salt use also holds methodologic importance, because this source is often viewed as an index of total sodium intake. We found that only a mean of 17% of salt missing from preweighed shakers was actually ingested. This value is consistent with reports of 24% from England,[26] and 29% from Italy.[27] This may account for the poor correlation between discretionary and total sodium intake noted in empirical studies.[24,26]

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Improvement of Automated Electrocardiographic Diagnosis by Combination of Computer Interpretations of the Electrocardiogram and Vectorcardiogram

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In the international project "Common Standards for Quantitative Electrocardiography" (CSE), diagnostic results of different computer programs for the interpretation of the electrocardiogram (ECG) and of the vectorcardiogram (VCG) were combined, and it was shown that the "combined program" performs better than each program separately. Because the program MEANS (Modular ECG Analysis System) comprises 2 different classification programs — one for the ECG, the other for the VCG — this allowed investigation of whether the combined interpretations would yield a better diagnostic result than either one separately. This approach requires that a VCG always be recorded in addition to the ECG. To circumvent this complication, the VCG was reconstructed from the simultaneously recorded ECG leads. This reconstructed VCG was then interpreted by the VCG classification program, whereupon the diagnostic interpretations of the ECG and the reconstructed VCG were combined. For the validation, the CSE database of documented ECGs and VCGs (n = 1,220) was used.

The combination of the ECG and VCG interpretations yielded a better diagnostic result than each interpretation program separately (total accuracy 74.2% (ECG + VCG) vs 69.8% (ECG) and 70.2% (VCG), p <0.001 in both cases). The results for the reconstructed VCG (total accuracy 70.5%) are comparable to those for the ECG and the VCG (p >0.10 in both cases). The performance of the combined interpretations of ECG and reconstructed VCG (total accuracy 73.6%) is approximately the same as that of the combined ECG and VCG (p

>0.10). Thus, the performance of an ECG computer program can be improved by incorporating both ECG and VCG classificatory knowledge, using only the ECG itself.

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"Two heads are better than one" is a saying that also appears to hold for the interpretation of the electrocardiogram (ECG) — and perhaps the more heads the better. In the international project "Common Standards for Quantitative Electrocardiography" (CSE)[1] it was shown that a "synthetic ECG diagnostician," produced by merging the interpretations of 8 ECG readers, performed better than each reader separately.[2,3] The same proved to be the case for computer programs for the interpretation of the ECG or of the vectorcardiogram (VCG). In the present study, we sought to take advantage of this effect to improve the results of the ECG computer program MEANS (Modular ECG Analysis System).[4] This is feasible because MEANS comprises 2 different classification programs: One for the ECG, the other for the VCG. The combination of the 2 may then possibly yield a better result than that of either one separately. The obvious objection that this approach requires, that a VCG always be recorded in addition to the routine 12-lead ECG, can be met by a technical artifice: It is possible to synthesize the VCG from the simultaneously recorded ECG leads.[5] The reconstructed VCG is a near-replica of the authentic (Frank) VCG and can be processed in the usual way by the VCG classification program. We will show that combining the computer interpretations of the ECG and the VCG indeed improves diagnostic accuracy, and that equally good results are obtained when the reconstructed VCG replaces the VCG.

METHODS

Database: For testing purposes, the diagnostic database that was collected in the CSE project[1,6] was used. This database consists of 1,220 ECG and VCG recordings. In each case, all leads of the ECG and VCG were recorded simultaneously at a sampling rate of 500 Hz during 8 or 10 seconds. All cases have been validated by

ECG-independent clinical evidence, such as echocardiography, enzyme levels, and so forth.[6,7] The following 8 main categories were distinguished: left ventricular hypertrophy (n = 183), right ventricular hypertrophy (n = 55), biventricular hypertrophy (n = 53), anterior infarction (n = 170), inferior infarction (n = 273), combined infarction (n = 73), infarction with manifest hypertrophy (n = 31), and normal (n = 382). The normal group included "ambulatory" normal subjects (n = 286) and "catheterized" normal subjects (n = 96). Major conduction defects, such as complete right and left bundle branch block, were excluded, as were complex rhythm disturbances. Each case in the database was also read independently by 9 cardiologists (ECGs read by 8, VCGs read by 5). For every case, the cardiologists' interpretations were combined. This "combined cardiologist" result served as another reference set in the present study. Both the "clinical evidence" and the combined cardiologist result is classified information that remains under lock and key at the CSE coordinating center. Thus, an independent database for testing ECG computer programs can be maintained.

Computer program: The MEANS program was used for our investigations. In its signal-analysis part, one and the same algorithm is employed to process the 12-lead ECG (using 3 reconstructed orthogonal leads) or the VCG.[4] The classification parts of the ECG and VCG programs use a heuristic approach by means of decision-tree logic.

Reconstruction: Each of the 3 VCG leads, X, Y and Z, can be reconstructed through a linear combination of ECG leads, i.e., by multiplying each of the 8 independent simultaneously recorded ECG leads with an appropriate coefficient and adding the re-scaled leads. The reconstruction coefficients were derived using multivariate regression.[5]

Coding of diagnostic results: The statements produced by the ECG and VCG classification parts of MEANS were rendered into diagnostic codes according to the CSE coding scheme.[6,7] A code comprises a diagnostic category and a qualifier. The pathologic categories are left ventricular hypertrophy, anterior infarction, and so on, corresponding to the diagnostic groups in the clinical database. When the program stated a major conduction defect (a category not present in the database) as a single statement, the case was mapped to a category "other." When the program cited none of the major pathologic categories but only non-major abnormalities such as ST-T changes, left anterior or posterior fascicular block, and so forth, the CSE rules prescribe mapping to the "normal" category. The normal category thus contains electrocardiographically true normals as well as electrocardiographically abnormals that could not be mapped to 1 of the available pathologic categories. Further, 1 of 3 qualifiers had to be used: definite, probable or possible.

Combination of diagnostic results: The same method that was used in the CSE project to merge results from different observers or different programs into a combined interpretation has been applied in the present study to combine the computer interpretations of the ECG and VCG, and of the ECG and reconstructed

VCG. The qualifier in each diagnostic code is assigned points corresponding to the level of certainty: "definite" 3 points, "probable" 2 points, and "possible" 1 point (which one may interpret to correspond with probabilities of 1, ⅔, and ⅓, respectively). This is done separately for the interpretation of each reader or each program. The combined interpretation for a particular case is then determined by adding the qualifier points of corresponding categories over the contributing readers or programs, and dividing by their number. The resulting value, between 0 and 3, is then rounded. For instance, when in our study the ECG program would list: "probable (=2) left ventricular hypertrophy" and the VCG program: "possible (=1) left ventricular hypertrophy, probable (=2) anterior infarction," the combined interpretation result would be: "probable ((2+1)/2→2) left ventricular hypertrophy, possible ((0+2)/2→1) anterior infarction."

Classification matrixes: In the CSE coordinating center, our computer results were compared with the

TABLE I Results (%) for the Computer Interpretation of the Electrocardiogram, the Vectorcardiogram, and the Reconstructed Vectorcardiogram, and for the Combined Interpretations of the Electrocardiogram and Vectorcardiogram, and the Electrocardiogram and Reconstructed Vectorcardiogram*

Computer Interpretation	Clinical Evidence		
	Normal (n = 382)	Hypertrophy (n = 291)	Infarction (n = 547)
Electrocardiogram			
Normal	97.1 (371.0)†	43.0 (125.0)	26.5 (145.0)
Hypertrophy	0.3 (1.0)	42.5 (123.8)	2.5 (13.8)
Infarction	2.6 (10.0)	9.1 (26.5)	67.2 (367.8)
Other	0.0 (0.0)	5.4 (15.8)	3.7 (20.5)
Vectorcardiogram			
Normal	86.6 (331.0)	28.9 (84.0)	16.5 (90.0)
Hypertrophy	1.6 (6.0)	45.8 (133.4)	2.3 (12.5)
Infarction	11.3 (43.0)	19.7 (57.3)	76.0 (415.5)
Other	0.5 (2.0)	5.6 (16.3)	5.3 (29.0)
Reconstructed vectorcardiogram			
Normal	94.0 (359.0)	31.3 (91.0)	20.7 (113.0)
Hypertrophy	1.6 (6.0)	46.3 (134.8)	3.0 (16.3)
Infarction	4.2 (16.0)	16.7 (48.5)	70.2 (384.2)
Other	0.3 (1.0)	5.8 (16.8)	6.1 (33.5)
Electrocardiogram and vectorcardiogram			
Normal	91.6 (350.0)	28.7 (83.5)	16.9 (92.5)
Hypertrophy	0.7 (2.5)	49.1 (142.8)	1.9 (10.3)
Infarction	7.7 (29.5)	17.9 (52.2)	77.9 (426.2)
Other	0.0 (0.0)	4.3 (12.5)	3.3 (18.0)
Electrocardiogram and reconstructed vectorcardiogram			
Normal	94.4 (360.5)	30.9 (89.8)	19.8 (108.4)
Hypertrophy	1.3 (5.0)	49.7 (144.7)	2.5 (13.5)
Infarction	4.1 (15.5)	14.9 (43.5)	74.4 (407.1)
Other	0.3 (1.0)	4.5 (13.0)	3.3 (18.0)

*The percentage of correct classifications for each category is underlined. Noninteger values may result from the Common Standards for Quantitative Electrocardiography procedure that maps program statements into diagnostic categories (see Methods Section).

clinical evidence and with the combined cardiologist. The CSE approach has been to score by case rather than by diagnostic category. Thus, each case contributes 1 single point to a classification matrix. If more than 1 diagnostic category is associated with a particular case, only the category with the highest degree of certainty is counted. If ≥ 2 categories have equal qualifiers at the highest level, the 1 point to be allotted is evenly divided over the appropriate cells of the classification matrix. Cases with biventricular hypertrophy, combined infarction, or a combination of hypertrophy and infarction, are subject to different mapping schemes, the details of which have been described previously.[7] Briefly, a case with biventricular hypertrophy is counted as partially correct when it was classified as left or right ventricular hypertrophy, i.e., half of the point will be allotted to the category biventricular hypertrophy and the other half to category "other." Likewise, cases with combined infarction or with a combination of hypertrophy and infarction are counted as partially correct when 1 of the constituent categories was cited.

RESULTS

Taking either the clinical evidence or the combined cardiologist as a reference, classification matrixes were computed for the computer interpretation of the ECG, the VCG and the reconstructed VCG, and for the combined interpretations of the ECG and VCG, and the ECG and reconstructed VCG. From these 8-by-8 matrixes, 3-by-3 matrixes were derived for the categories normal, hypertrophy (including left, right, and biventricular hypertrophy), and infarction (including anterior, inferior, mixed infarction and infarction with manifest hypertrophy).

The 3-by-3 classification matrix of each computer interpretation against the clinical evidence is given in Table I. The specificity, i.e., the percentage of normal cases correctly classified as such by the computer, is highest for the ECG interpretation (97.1%); the combined interpretations of ECG and VCG yield a specificity of 91.6% (p <0.001, equivalence tested with Wilcoxon's signed-rank test[8]), and the combined interpretations of ECG and reconstructed VCG a specificity of 94.4% (p = 0.003). The sensitivities for hypertrophy and infarction of the combined interpretations of the ECG and VCG, and of the ECG and reconstructed VCG, are significantly higher than those of the ECG interpretation (p <0.001 in both cases).

Total accuracy, i.e., the overall percent correct classifications, was computed for each interpretation program from the 8-by-8 classification matrix of all main categories. Taking the clinical evidence as the reference, the total accuracy for the ECG was 69.8%, for the VCG 70.2%, for the reconstructed VCG 70.5%, for the ECG and VCG combined 74.2%, and for the ECG and reconstructed VCG combined 73.6%; taking the combined cardiologist as the reference, total accuracies were 80.3, 78.1, 79.0, 84.1 and 83.3%, respectively. For both references, the total accuracies of the combined interpretations proved to be significantly higher than those of the individual interpretations (p <0.001 in all cases). These total accuracies have been entered in the scatter plot of Figure 1, together with those of the individual cardiologists from whom the combined cardiologist was derived, and of the other interpretation programs that participated in the CSE study.[7]

Total accuracy depends on the composition of the database. In the CSE database, about 30% of the cases
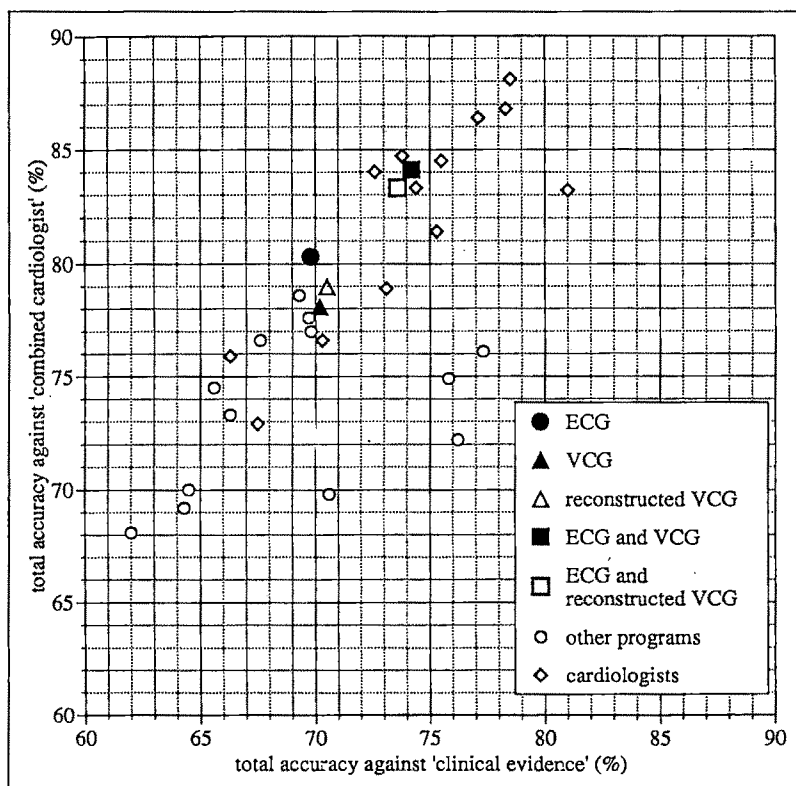
FIGURE 1. Total accuracies for the computer interpretation of the electrocardiogram (ECG), the vectorcardiogram (VCG), and the reconstructed VCG, and the combined interpretations of the ECG and VCG, and the ECG and reconstructed VCG. Also, the total accuracies of the other programs and of the cardiologists participating in the Common Standards for Quantitative Electrocardiography study have been plotted. From these cardiologists the 'combined cardiologist' was derived. All interpretation results are compared with the 'clinical evidence' *(horizontal)* and the 'combined cardiologist' *(vertical).*

- ● ECG
- ▲ VCG
- △ reconstructed VCG
- ■ ECG and VCG
- □ ECG and reconstructed VCG
- ○ other programs
- ◇ cardiologists

is normal according to clinical evidence. If the composition of the database would be shifted to contain more and more normal cases, a point would finally be reached where the total accuracy of the ECG interpretation would exceed that of any of the combined interpretations, as the ECG program shows highest specificity. We determined the total accuracies for different percentages of normal cases; the numbers of cases in the other categories were adjusted in proportion to the initial numbers in the CSE database. If the number of normal cases in the database stays under 62% (or 71%), the total accuracy of the combined interpretations of ECG and VCG (or ECG and reconstructed VCG) remains larger than that of the ECG interpretation.

DISCUSSION

"Two heads are better than one," and apparently this saying holds for our ECG and VCG (or reconstructed VCG) computer interpretations, for at least the total accuracies (Figure 1). The sensitivities for hypertrophy and infarction are also better, but the specificity is in between.

Under what conditions, then, do 2 "observers" (cardiologists or programs) perform better than each one separately given certain combination rules, in this case those of the CSE project? There are several mechanisms involved. In the first place, one can choose from >1 qualifier to grade a case. Thus, a case may be called "definite X" by one observer and "possible X, probable non-X" by the other. Let X be the correct diagnosis. The first observer then classified correctly, the second incorrectly because the CSE procedure only uses the highest ranking statement, namely "probable non-X." However, the combination would score "probable (= $(3+1)/2\rightarrow2$) X, possible (=$(0+2)/2\rightarrow1$) non-X," and 1 full point would be allocated to X in the classification matrix. If only 1 qualifier (definite) were admitted, the point would have been split between the equal ranking "definite X" by the first and "definite non-X" by the second observer. There is also a second mechanism: The diagnosis is not restricted to 1 category X or its negation non-X, but non-X may contain Y, Z, etc. (These categories need not be mutually exclusive.) We may have "probable X, possible Y" by the one observer and "possible X, probable Z" by the other. This combines to "probable X, possible Y, possible Z," and again the full point will be salvaged for the correct diagnosis X.

The basis of the first mechanism is that a correct interpretation is made with more confidence than the incorrect one. The basis of the second mechanism is that if observers are hesitant about the correct diagnosis they will still mention it, although perhaps at a lower level of certainty, but, given a choice of wrong interpretations, their alternatives scatter over the other options and thus cancel out.

In the present study, we integrated 2 classification programs at the level of their outputs, i.e., their diagnostic statements. This approach is simple, but it is also a rather crude and indirect way of combining diagnostic classification knowledge. A more direct combination

procedure would be to integrate into 1 program the qualities of the ECG and VCG approaches. Such a selective combination of knowledge requires a precise understanding of the strong and weak points in the classification logic and is an issue for further research.

Our computer interpretation results are gauged both against the combined cardiologist and the clinical evidence. One may question how the combined cardiologist can stand up against the clinical evidence. It may be argued that the ECG is an independent source of information. Even if all clinical evidence would say normal and the ECG is abnormal in the cardiologic eye (and thus in that of a program that is based on cardiologic conceptions), this might not mean that cardiologists are wrong. (They would only be wrong if they would take the interpretation of the ECG to be the final diagnosis without considering other evidence.) Therefore, we believed it interesting to see how far a program succeeds in mimicking the human expert.

Because the reconstructed VCG, being nothing more than a mathematic conversion, contains only the electrical information enclosed in the ECG, it is remarkable that processing the same information, first in the form of the ECG, then, after its mathematic conversion, in the form of the VCG, should yield results that are able to improve on each other when combined. This suggests that representing and processing the signals in VCG form utilizes information that is neglected in ECG interpretation, presumably information on phase relationships between the ECG signals. Conversely, the ECG carries proximity information that is probably lost in the VCG approach. The practical implication of all this is that the performance of an ECG computer program can be improved by applying VCG criteria to the very ECG data.

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Aggravation of Arrhythmia by Antiarrhythmic Drugs, and the Important Role of Underlying Ischemia

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It has been recognized that antiarrhythmic agents, although intended to prevent or limit arrhythmia, may actually cause an unexpected and unpredictable worsening of arrhythmia.[1] Reported risk factors for this complication include significantly reduced left ventricular function, congestive heart failure and history of sustained ventricular tachyarrhythmia.[2] The results of the Cardiac Arrhythmia Suppression Trial (CAST)[3] increased concerns about arrhythmia aggravation, because 2 widely used antiarrhythmic agents resulted in an increased mortality when administered to patients with a recent myocardial infarction and no overt congestive heart failure who had frequent but only single ventricular premature beats.

In CAST, the increase in mortality was observed in all patient groups analyzed, but was especially significant in those with several previous infarctions and a subendocardial infarction. In these patients, the risk of arrhythmia aggravation was as high (risk ratio 3.4) as that observed in those with more severe disease, substantial left ventricular dysfunction and history of serious arrhythmia. Furthermore, the occurrence of proarrhythmia, previously reported to be an early complication with antiarrhythmic drugs, was observed throughout the entire follow-up period and was also a late event. Patients exhibited "late" proarrhythmia despite initial suppression of spontaneous ventricular arrhythmia during the titration phase of the study. It is likely that during follow-up, myocardial remodeling and healing altered the underlying substrate, affecting the action of these drugs. One proposed hypothesis is that these patients had ongoing myocardial ischemia that further modified the underlying myocardial substrate, and transiently converted a stable myocardium into 1 that was unstable and potentially arrhythmogenic, capable of generating and supporting a reentrant arrhythmia. In the case of ischemia, the presence of antiarrhythmic drugs may further enhance this potential and is perhaps more likely to result in arrhythmia aggravation.

It has been observed that during acute coronary occlusion, there is spatial heterogeneity of blood flow between ischemic and nonischemic tissue. Several investigators proposed that this can even occur in a normal heart, but to a such smaller degree. Marcus et al[4] studied the spatial distribution of left ventricular perfusion in 24 awake dogs using radio-labeled microspheres. At the conclusion of the infusion, the left ventricular myo-

cardium was divided into 4 regions, each with 8 segments. Each segment was divided in 3 layers: endocardium, myocardium and epicardium. The investigators observed that there was spatial inhomogeneity of blood flow among different segments and layers. Mean dispersion of blood flow was 21.4% in all the dogs.

These regional inhomogeneities are augmented when myocardial ischemia occurs as a result of a reduction in blood flow. In an animal model, Coggins et al[5] regulated blood flow through the left main coronary artery to produce perfusion pressures of 70, 50, 40 and 30 mm Hg. Regional blood flow at these arterial pressures was assessed at rest and during the infusion of adenosine, a pharmacologic vasodilator that permits measurement of coronary artery flow reserve. At a perfusion pressure of 70 mm Hg, virtually all segments had intact flow reserve, and as perfusion pressure progressively decreased to 50, 40 and 30 mm Hg, the ability to increase flow in response to adenosine was observed in 92, 55 and 8% of all regions, respectively. Furthermore, flow reserve was greater in the epicardium than in the endocardium. These results indicate that with ischemia, there is a significant, nonuniform reduction of regional flow that produces marked heterogeneity of blood and oxygen supply to even small areas of the myocardium.

Myocardial ischemia produces a number of metabolic changes including an increase in extracellular potassium concentration and a decrease in tissue pH, which alter local myocardial electrophysiologic properties. In dogs, Hill and Gettes[6] reported the effect of an increase in extracellular potassium on the resting membrane potential and myocardial conduction velocity. When potassium was infused directly in the animal or when the entire ventricle was made ischemic, the global and homogeneous increase in extracellular potassium levels produced a generalized and uniform increase (less negative) in resting myocardial membrane potential, a reduction in upstroke velocity (Vmax) of phase 0, and a reduction in membrane conduction velocity (or increase in activation time). With left anterior descending coronary artery occlusion and the development of regional ischemia, there was a rapid increase of extracellular potassium concentration within the ischemic zone, but no change in nonischemic tissue. Concentration of extracellular potassium in the center (most ischemic) of the ischemic zone was significantly greater than at its margins. Furthermore, ischemia and the extracellular potassium levels were increased in the endocardium compared with in the epicardium. The increase in resting membrane potential, the reduction in phase 0 Vmax, the slowing of impulse conduction velocity, and the lengthening of the activation time within the myocardi-

um correlate with the change in potassium concentrations and are therefore also inhomogeneous. The investigators further observed that the electrophysiologic changes due to ischemia were greater than those during the controlled infusion of potassium, although the extracellular potassium levels achieved were equivalent, suggesting that other factors caused by ischemia have a role.

One important factor is tissue acidosis, which is also produced by ischemia. Kagiyama et al[7] studied the effects of different potassium and hydrogen ion concentrations on the action potential and membrane conduction velocity. Ischemically mediated acidosis and increase in extracellular potassium concentration exerted independent effects on Vmax of the action potential, membrane conduction velocity and activation time. Acidosis resulted in a nonlinear reduction in Vmax, and a decrease in myocardial conduction velocity, regardless of the potassium concentrations. Therefore, the overall effect of acute ischemia is due to the combined effects of acidosis and the increase in extracellular potassium.

Watanabe et al[8] also observed that with the reduction of coronary blood flow, and development of ischemia, the resultant metabolic and electrophysiologic changes were more pronounced in the deeper layers of the myocardium (particularly the endocardium) than in the epicardial layer. In addition to the effect of hyperkalemia on Vmax and conduction velocity, the increase in extracellular potassium causes a shortening of membrane refractory period.[9] Therefore, the nonuniformity in extracellular potassium levels will cause heterogeneity in membrane activation times and action potential duration, an increased dispersion of refractoriness (an important precondition for reentry).

These ischemically mediated changes also have important implications for the action of membrane active (class 1) antiarrhythmic agents that, like hyperkalemia and acidosis, slow conduction. These drugs may have more significant effects in ischemic than in normal tissue, further enhancing differences between ischemic and nonischemic areas. It has also been reported that some of these agents have differential effects on Purkinje fibers and ventricular muscle, which further augments their arrhythmogenic potential.[10] Furthermore, nonuniform reductions in blood flow can cause differences in regional distribution, clearance and tissue con-

centrations of antiarrhythmic drugs. Nattel et al[11] studied the effects of left anterior descending occlusion on the tissue concentrations and action of aprinidine, a lidocaine-like antiarrhythmic drug. Aprinidine was administered to dogs before, 5 minutes after and 24 hours after occlusion. When administered before occlusion, the clearance rate of aprinidine from the ischemic zone was markedly impaired, and its concentration in this zone was twofold higher than within the nonischemic tissue. When aprinidine was administered after occlusion, there was only a slow and gradual increase in tissue concentration within the ischemic zone compared with in the normal tissue. A sustained ventricular tachyarrhythmia occurred in 49% of dogs who received aprinidine before occlusion, compared with 14% in dogs receiving aprinidine after occlusion, and 10% in dogs not receiving aprinidine therapy. The investigators postulated that as a result of differences in blood flow and drug clearance, there is a disparity in regional drug concentrations and hence heterogeneity in the degree of electrophysiologic effects that influence the initiation and maintenance of ventricular arrhythmia. Of particular interest, dogs that were pretreated with the antiarrhythmic agent before the development of ischemia had the highest incidence of ventricular tachycardia, suggesting a proarrhythmic action of the drug in the setting of ischemia. The data are further supported by a report by Elharrar et al[12] who observed that in the ischemic myocardium, aprinidine resulted in a slowing of impulse conduction, and delay in activation time, which were significantly greater than with ischemia alone.

Changes in potassium and pH can also alter drug action. Singh and Williams[13] reported that changes in potassium levels affect changes in Vmax and hence conduction velocity produced by antiarrhythmic drugs. In an animal treated with lidocaine and phenytoin, they observed that the drug-related slowing of Vmax was altered by changes in potassium level and that the concentration of drug necessary to reduce Vmax was indirectly related to the tissue potassium level.

In view of the data from these studies, the following scheme of drug-induced aggravation of arrhythmia provoked by ischemia is proposed. Coronary artery disease results in marked variation in perfusion pressures and blood flow to adjacent segments of myocardium. This causes regional difference in tissue concentration of

FIGURE 1. Theoretic mechanism for enhanced potential of reentrant arrhythmia in ischemic tissue. Changes in potassium (K+) and pH alter action potential and electrophysiologic properties, creating differences between normal and ischemic tissue, as well as between epicardium and endocardium within ischemic region. These differences in electrophysiologic parameters may be enhanced by antiarrhythmic drugs.
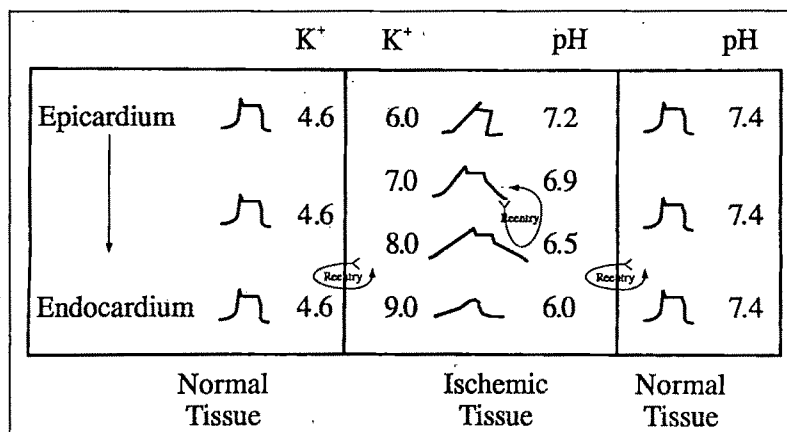
drug and in inhomogeneity of electrophysiologic parameters even during baseline, nonischemic conditions. With ischemia, regional inhomogeneity is further enhanced, and there is also disparity within the ischemic zone (the epicardium receiving the least amount of blood flow and oxygen). Distribution, binding and clearance of antiarrhythmic drugs are affected and occur in a heterogeneous fashion. Extracellular potassium concentrations increase, and tissue pH decreases, altering local membrane electrophysiologic properties, particularly the resting membrane potential, Vmax of the action potential upstroke (phase 0), membrane conduction velocity or activation time, and refractory periods. The metabolic changes and dispersion of electrical properties occur not only between adjacent segments, but also transmurally within each segment (Figure 1). These regional differences may be further enhanced by antiarrhythmic drugs, especially when tissue concentrations also vary. An antiarrhythmic drug that produces uniform effects under resting and nonischemic conditions will cause a significant amount of electrophysiologic heterogeneity during ischemia. These disparate local electrical properties provide the appropriate precondition or setting for arrhythmia aggravation. Thus, a drug that is believed to be effective for arrhythmia suppression in a resting, nonischemic state may result in proarrhythmia during ischemia.

Based on the previous observations it is likely that in the postinfarction healing period, the presence of a changing substrate and episodic ischemia alters the action of an antiarrhythmic drug. An agent that is initially effective may provoke arrhythmia at a later point in time. This has important implications regarding the use of antiarrhythmic drugs in patients with underlying coronary artery disease who are likely to have transient, active ischemia that may be overt or silent. In these patients antiarrhythmic therapy should be evaluated at rest, as well as during physical exertion. Exercise testing is a physiologic way of producing ischemia and activation of the sympathetic nervous system, resulting in the metabolic, electrolyte and electrophysical alterations that may interact with, potentiate or interfere with antiarrhythmic drug action.[14]

In conclusion, each antiarrhythmic agent has the potential for proarrhythmia. This is most often seen in patients with more extensive myocardial damage, poor left ventricular function and history of sustained ventricular tachycardia. Another important factor is ischemia. These agents should be used cautiously in patients with evidence of overt or silent ischemia, and these effects should be completely evaluated under different circumstances.

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Reduction of QT-Interval Imprecision and Variance by Measuring the JT Interval

David H. Spodick, MD, DSc

The QT interval, a surrogate for the ventricular transmembrane cellular action potential, has had a long and useful history as a noninvasive correlate of an increasingly investigated range of applications, including metabolic and drug effects and toxicities, prediction of malignant ventricular arrhythmias and sudden cardiac death, exercise and autonomic nervous system responses, general myocardial condition (e.g., ischemia) and the design of physiologically adaptive cardiac pacemakers.[1-6] Together with other cardiac time intervals, the QT interval has a complex relation to heart rate (expressed as cardiac cycle length or beats/min). This relation has produced a remarkable variety of formulas for the QT-RR and QT-HR relations, including square root, cube root, exponential, logarithmic and even linear.[7,8] However, at high heart rates, correlation of QT and cycle length is spurious, because most of the cycle is, indeed, QT, so that it becomes a virtual self-correlate.[7] However, rate-corrected QT interval (QTc), particularly by the original Bazett formula of 1920,[9] has remained useful for the applications mentioned. A particularly apt example is the demonstration that QT correction by Bazett's formula to <400 ms (0.4 second) in the presence of inverted T waves is a reliable indication of digitalis effect.[10] However, a stronger primary T-wave change can override the QT-shortening effect of digitalis.[11] These and many other examples emphasize the T wave as the source of primary QT changes, and it is apparent that the JT portion of the QT interval is the responsible element, changes in QRS being either nonexistent or too small to detect. (Factors such as drugs and toxic agents prolonging the QRS will be detected in the standard QRS measurement.)

The upper limit of normal QTc by the Bazett formula can be found in quick-reference tables or is variously reported (e.g., not ≤0.42 in men, ≤0.43 in women,[12] or ≤0.425 overall).[1] Regardless of the limit selected, it is clear that for this most common correction formula, the range will be narrow.[13,14]

Because the JT portion of the QT interval is almost always the significant portion, determination of normal values for the JT interval appears to be overdue. The problem is broadly recognized in the presence of bundle branch block,[12] but QRS variability within the normal QRS range is the principal problem. The vast majority of normal QRS intervals are between 0.07 and 0.09 or 0.1 second (70 to 100 ms), and distinctively narrow QRS intervals are found frequently in obstructive lung disease patients (often 0.06 or even 0.05 second)[15] who often receive QT (JT)-prolonging medication. Thus, it becomes clear that patients with shorter QRS durations at baseline (before intervention or pathologic influence) can have increased QT intervals by 30 to 40 ms before QT prolongation is recognizable; in contrast, their JT intervals will demonstrate this prolongation sensitively. Since QRS time is eliminated, therefore, it seems apparent that inclusion of the QRS should confound the measurement by contributing to absolute and intersubject QT variance.

It should be relatively easy to obtain normal standards for JT-cycle length relations from normal population data already available in computerized electrocardiographic data bases. Irrespective of the final "rate correction" formulas, subtraction of the QRS from the QT interval should be straightforward in such epidemiologic material, yielding potentially more precise and less variant, and hence more appropriate, normal data.

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Stenting for Elastic Recoil During Coronary Angioplasty of the Left Main Coronary Artery

Carlos Macaya, MD, Fernando Alfonso, MD, Andrés Iñiguez, MD, Javier Goicolea, MD, Rosa Hernandez, MD, and Pedro Zarco, MD

onventional percutaneous transluminal coronary angioplasty (PTCA) of the left main coronary artery (LMCA) constitutes a therapeutic challenge because it is associated with significant immediate morbidity and mortality and a high restenosis rate.[1-4] Special difficulties may arise during PTCA of ostial LMCA lesions including technical problems concerning precise balloon location and the possible appearance of elastic recoil despite the use of adequate-sized balloons.[4] We report 3 patients with "unprotected" ostial lesions of the LMCA in whom significant elastic recoil after PTCA was successfully managed with coronary stenting. In each patient the strategy for stent deployment consisted in leaving the proximal edge of the stent slightly protruding into the aortic root. This was successfully accomplished and subsequently confirmed in the 3 cases.

Of 10 consecutive patients undergoing conventional balloon PTCA of the LMCA in our institution, 3 required a stent implantation (Palmaz-Schatz) for elastic recoil of an ostial LMCA lesion. Baseline characteristics of these 3 patients are summarized in Table I. The 3 patients had refractory angina at rest despite multiple attempts to optimize medical therapy. All patients were at a prohibitive surgical risk.[4,5] Patient 1 had a terminal epidermoid carcinoma of the lung. Patient 2 was in refractory cardiogenic shock, resulting from an early occlusion of a saphenous bypass graft to the left anterior descending coronary artery which caused a perioperative anterior myocardial infarction. Patient 3 had previously undergone 3 cardiac interventions including an open mitral valve commissurotomy followed by 2 mitroaortic valve replacements for severe rheumatic valve disease (the last 6 months before, with implantation of 2 St. Jude [nos. 25 and 21] prostheses). A long recovery period with difficulties to wean the patient off from the mechanical ventilator and an associated mediastinitis

complicated this intervention and, subsequently, he was admitted again for bifemoral bypass grafting. In every patient PTCA of the unprotected LMCA was eventually considered the therapy of choice. Lesion narrowing was measured with electronic calipers from a digital automatic angiographic system (Phillips DCI). All patients had severe stenosis of the ostium of the LMCA (Figures 1 to 3). Intracoronary nitroglycerine (0.2 mg) was administered before the procedure. A balloon PTCA was initially attempted in every case. A perfusion balloon (Stack) was used in patient 1, whereas patient 2 underwent PTCA while receiving percutaneous cardiopulmonary support (CPS, USCI-Bard). In this patient the pulsatile pressure wave morphology changed to a continuous lineal pressure of 75 mm Hg during balloon inflation. Aortobifemoral bypass grafting prevented the use of cardiopulmonary support in patient 3. During PTCAs care was taken to use short inflation times (<15 seconds) and to achieve a nonselective engagement of the left coronary ostium in order to allow maximal coronary flow between balloon inflations (ranging from 2 to 3) and to document, with gentle flushing of contrast through the guiding catheter, that the proximal part of the balloon was indeed inflated in the ostial portion of the LMCA. In every case, the "waist" of the balloon disappeared at complete balloon expansion (maximal pressures of 8, 6 and 7 atm, respectively) but the narrowing of the LMCA recurred to 74, 71 and 55%, respectively, after balloon deflation. In our first patient a stent was considered to be the device of choice after PTCA failure because of the presence of a large calcified atherosclerotic plaque overlying the LMCA (Figure 1), whereas in the next 2 cases the possibility of stenting was contemplated and organized before PTCA (standby stenting). In all cases the LMCA was considered of enough length to accommodate the stent. Stenting was successful in every patient — residual stenosis <20% (Figures 1 to 3) — and no procedural related complications occurred. All patients were discharged asymptomatic after 10 to 14 days of anticoagulation with heparin. After stenting, patients 2 and 3 received conventional treatment but hemoptysis prevent-

TABLE I Baseline Clinical and Angiographic Characteristics in the Three Men with Unstable Angina

Pt.	Age (yr)	Previous MI	Previous Cardiac Surgery	LMCA (%)	Additional Narrowings		EF (%)	LVEDP (mm Hg)
					RC Artery	LAD		
1	60	Anterior	0	86	47%	63%	62	29
2	69*	Anterior Inferior	Bypass	88	100%	0	31	42
3	56	0	Prostheses	74†	0	0	—	—

*Cardiogenic shock.
†Left coronary artery dominance.
EF = angiographic left ventricular ejection fraction; LAD = left anterior descending coronary artery; LMCA = stenosis of the left main coronary artery; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction; RC = right coronary artery.

ed the use of coumadin in patient 1. Although this patient remained without angina for 4 months he eventually died from his pulmonary carcinoma. Pathologic examination disclosed a widely patent stent completely endothelized protruding 2 mm into the aortic root (Figure 1, bottom). In patients 2 and 3 an echocardiographic examination (short-axis view) demonstrated that the proximal part of the stent slightly protruded (1 and 2 mm, respectively) into the aortic root (Figures 2 and 3, bottom). Both patients have remained asymptomatic at 3 and 4 months follow-up, respectively. In patient 2 an improvement in the echocardiographically determined left ventricular ejection fraction (35 to 50%) was readily appreciated in serial studies.

Our findings suggest that coronary stenting provides an attractive therapeutic tool for patients with ostial LMCA lesions in whom elastic recoil is documented immediately after balloon deflation. The presence of a high content in elastic fibers in the proximal segment of the LMCA has been proposed as a mechanism to explain the possible appearance of elastic recoil and the high restenosis rate of conventional PTCA at this site.[2] The presence of calcium in our patient 1 also may have been operative

in this regard. The demonstration of elastic recoil in ostial LMCA lesions requires both using a balloon of appropriate size (with respect to the distal segment of the LMCA) and excluding displacement or a suboptimal positioning of the balloon at the time of maximal inflation. In this respect, once the guidewire has been advanced down into the distal left anterior descending coronary artery, the withdrawal of the guiding catheter to the left aortic sinus inducing a nonselective engagement of the left coronary ostium, constitutes a useful maneuver. This allows, first, a minimal reduction in coronary flow while the balloon catheter is being positioned and second, avoids the possibility of partial balloon inflation within the guiding catheter. Finally, this maneuver also permits contrast flushing through the guiding catheter during balloon inflation to document that the proximal part of the balloon protrudes into the aortic root. In our patients the stent was deployed after assuring that the ostial lesion was covered by the stent in all its length, as was subsequently confirmed in the 3 cases either during pathologic examination or by 2-
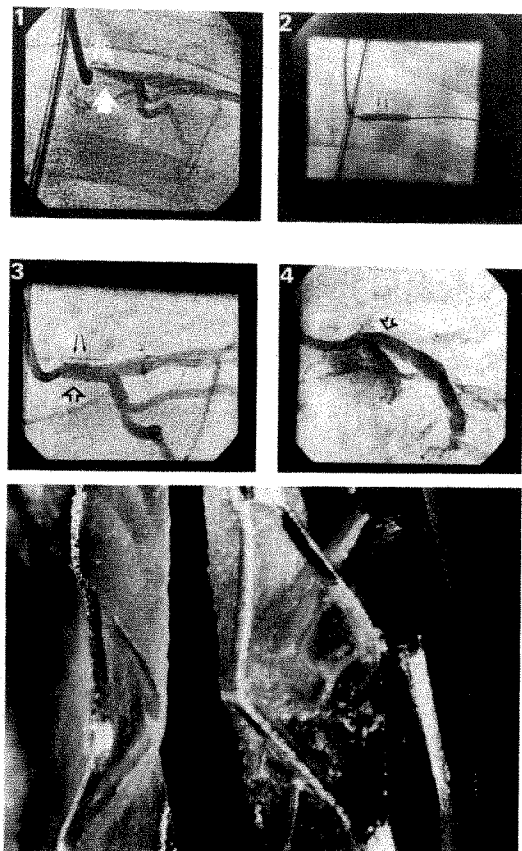
FIGURE 1. 1, right anterior oblique (15°) coronary angiogram showing a tight stenosis of the ostium of the left main coronary artery (large arrow) with some calcification overlying the lesion (small arrows). 2, balloon inflation after nonselective guiding-catheter engagement (small arrows denote calcium). The calcification was used as a landmark during dilatation. After stenting there is no residual stenosis. 3, right anterior oblique projection. 4, left anterior oblique (45°) projection with cranial (20°) angulation. Bottom, pathologic specimen of the stent opened along its longitudinal axis revealing a fully patent and completely endothelized stent.
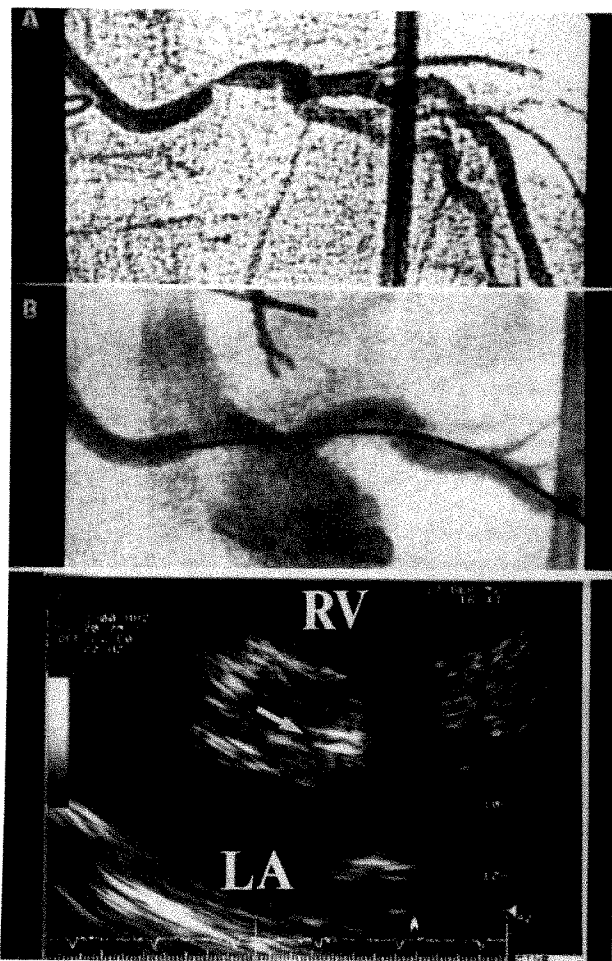
FIGURE 2. A, critical ostial lesion of the left main coronary artery from the right anterior (10°) oblique projection. B, left anterior oblique (20°) projection showing an optimal angiographic result after stenting. Note how contrast flushing is performed with the guidewire in place after nonselective engagement of the ostium with the guiding catheter to avoid stent damage. Bottom, echocardiographic study from the parasternal short-axis view revealing the stent (arrow) slightly protruding into the aortic lumen. LA = left atrium; RV = right ventricular outflow tract.

dimensional echocardiography. Other new technical devices, like atherectomy, may also emerge as attractive alternatives for treating elastic recoil of the LMCA but, in our experience, stenting provides a fast-to-implement resource and constitutes a very appealing tool especially for patients with unprotected LMCA lesions where time-saving is mandatory. Recently, the Task Force Report on Guidelines for PTCA has included unprotected LMCA as a contraindication for PTCA.[6] PTCA in this clinical setting should only be contemplated as a "last resort option" for critically ill patients with prohibitive operative risk.[4,5] However, we believe that the possibility of stenting (standby stenting) in case of PTCA failure or suboptimal result may increase the likelihood that PTCA will be offered with success to patients with LMCA disease. Percutaneous cardiopulmonary support may also facilitate stent deployment in these high-risk patients. Further studies are necessary to determine if stenting will constitute the approach of choice for selected patients with ostial LMCA lesions and also to assess if this therapeutic strategy will diminish the restenosis rate of LMCA lesions.

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FIGURE 3. *a,* left anterior oblique (45°) projection with cranial (20°) angulation revealing a severe stenosis in the ostium of the left main coronary artery *(arrow). b,* after conventional percutaneous transluminal coronary angioplasty significant (55%) residual stenosis persists. *c,* no significant residual stenosis is appreciated after coronary stenting. *Bottom,* echocardiographic study from the short-axis parasternal view of the aortic root just above the aortic valve cusps. A bright echodense structure protruding into the aortic root is shown at the 4 o'clock position *(arrow).* This image remained unchanged despite the use of slightly oblique cuts. Rv = right ventricular outflow tract.

Aspiration Thrombectomy for Removal of Coronary Thrombus

Guy S. Reeder, MD, Andre C. Lapeyre, MD, William D. Edwards, MD, and David R. Holmes, Jr., MD

Intracoronary thrombus is usually present in acute myocardial infarction and often in unstable angina.[1] At angioplasty, the presence of residual thrombus places the patient at increased risk for complications,[2,3] especially total occlusion. Heparin, aspirin and thrombolytic agents have been used to reduce the risk of occlusion, but with mixed results. We describe the use of suction aspiration to remove thrombus from a coronary stenosis before percutaneous transluminal coronary angioplasty (PTCA).

Selected patients with definite or probable intracoronary thrombus were identified at the time of elective or urgent PTCA, and at the discretion of the operator, suction/aspiration thrombectomy was performed before standard PTCA. Informed consent was obtained in all patients.

The technique of aspiration was as follows: After femoral arterial sheath placement and heparinization, an 8Fr guiding catheter was placed in the appropriate coronary ostium, and through this, a 0.014 to 0.018 guidewire and telescoping 5Fr miniguiding catheter (teleguide, Schneider U.S.A., Inc.) (Fig. 1) were inserted, and the teleguide was directed into the thrombus. The guidewire was removed, suction was manually applied to the teleguide with a 12 ml syringe, and the teleguide was

Pt. No.	Age (yr) & Sex	Presentation	No. of VD	Artery Treated	Duration of Occlusion	Thrombectomy Results	PTCA Results	Embolic Complications
1	62 F	AMI	2	Prox RCA	< 1 day	+	+	—
2	54 M	AMI	2	OM1	< 1 day	+	+	—
3	84 F	Recent MI	3	Mid RCA	3 days	—	+	—
4	70 M	AMI	2	Prox RCA	< 1 day	+	+	—
5	60 M	Angina	1	Prox RCA	60 days	—	NA	—
6	46 M	Recent MI	1	Mid LAD	3 days	—	+	—
7	36 M	Recent MI	1	Mid RCA	2 days	—	+	—
8	63 F	Recent MI	1	Prox RCA	6 days	+	+	—

AMI = acute myocardial infarction; LAD = left anterior descending; MI = myocardial infarction; NA = not applicable; OM1 = first obtuse marginal; Prox = proximal; PTCA = percutaneous transluminal coronary angicplasty; RCA = right coronary artery; VD = vessels diseases (70% diameter criterion); + = successful; — = unsuccessful.

withdrawn into the guiding catheter. The entire system was then removed from the patient with continued suction, and thrombus within the teleguide and adherent to its tip was removed. Catheters were flushed vigorously before reinsertion. The procedure was again performed if residual thrombus could be identified angiographically. In 2 cases of proximal (ostial) right coronary artery occlusion, direct aspiration of the guiding catheter was

performed as it protruded into the thrombus, and the teleguide was not used.

PTCA was then performed. Care was taken to note any evidence of distal embolization by repeat angiography at the completion of PTCA. Successful PTCA was defined as ≥40% luminal diameter enlargement, without subsequent death or emergency bypass surgery. Patients were also monitored closely for any evidence of systemic embolic events.
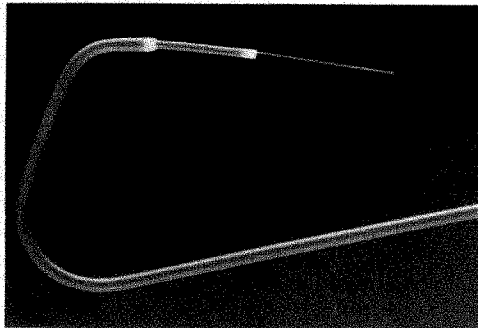
FIGURE 1. Catheter arrangement for aspiration thrombectomy. Judkin's 8Fr left guiding catheter contains 5Fr teleguide through which standard 0.018 inch guidewire has been placed. Teleguide moves freely within larger guiding catheter and can be advanced over wire into lesion containing thrombus.
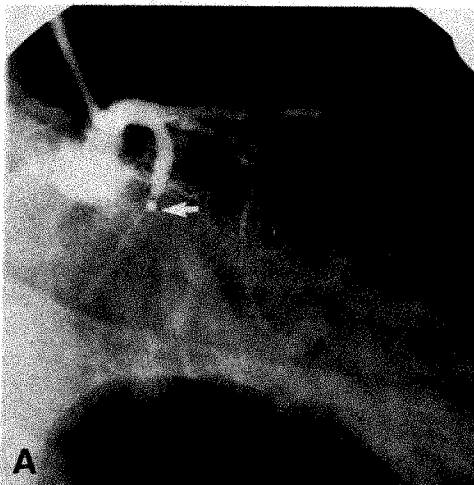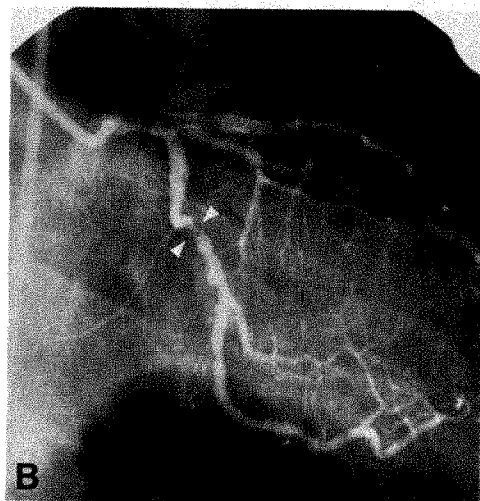
FIGURE 2. Aspiration thrombectomy (patient 2). A, right anterior oblique view; total occlusion of circumflex. Radio-opaque distal tip of teleguide (arrow) is inserted into occluding thrombus in circumflex. Guidewire has been withdrawn. B, contrast injection after aspiration of occluding thrombus. Flow to distal circumflex and branches has been restored. High-grade residual lesion (arrowheads). C, angiographic injection after successful angioplasty of this region. Excellent anterograde flow is present.

Eight patients with intracoronary thrombus studied by 1 of 3 operators underwent attempted aspiration thrombectomy. Patients were identified from 145 undergoing PTCA during the same 3-month period in our laboratory. Selection for PTCA, rather than thrombolysis, was at the discretion of the attending cardiologist and based on contemporary clinical judgment. Table I demonstrates the clinical and angiographic features of this patient group. Figures 2 and 3 show results in 2 successful cases.
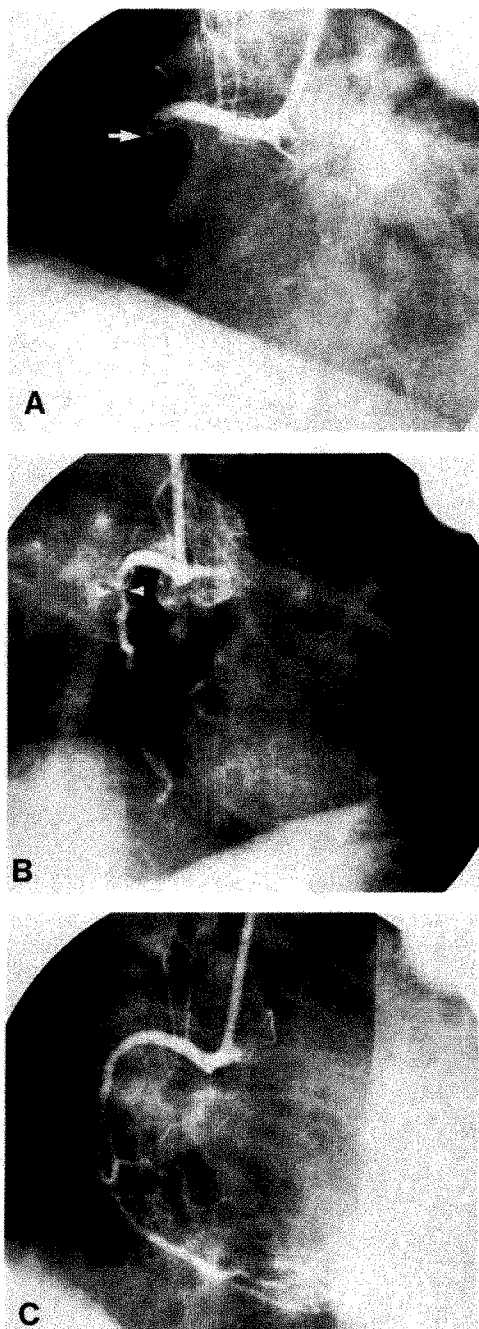
FIGURE 3. Aspiration thrombectomy (patient 4). *A*, angiogram in left anterior oblique orientation showing total occlusion of proximal right coronary artery *(arrow)*. *B*, angiogram in similar view after aspiration thrombectomy demonstrating restoration of flow and residual high-grade stenosis *(arrowheads)*. *C*, after angioplasty of this lesion, there is excellent anterograde flow with minimal stenosis.

Aspiration thrombectomy recovered thrombus material, and by itself restored flow to the previously occluded artery in 4 of 8 patients. The amount of thrombus recovered was variable, but usually did not exceed 1 to 2 mm in its largest dimension. In 1 patient with acute occlusion, reperfusion after thrombectomy alone was adequate to result in cessation of ischemic pain, despite persistence of a critical subtotal obstruction. Thrombectomy was successful in all 3 patients presenting with acute myocardial infarction and in 1 in whom coronary occlusion occurred 6 days before. Duration of occlusion in 4 unsuccessful thrombectomy cases was 3, 60, 3 and 2 days, respectively.

After attempted thrombectomy, patients underwent successful PTCA of the residual lesion in 7 of 8 cases. In 1 case, PTCA was not performed owing to the expressed wishes of the referring physician. No patient had evidence of either coronary or peripheral embolization during or after PTCA. No patient had in-hospital reocclusion of the dilated segment.

One-year follow-up was available in all 8 patients. No patient died or had subsequent bypass surgery. Three patients had subsequent PTCA (2 of these were successful thrombectomy cases). All 8 patients were asymptomatic at the last follow-up.

Aspiration thrombectomy was previously described in case reports,[4-10] but no series has been reported to date.
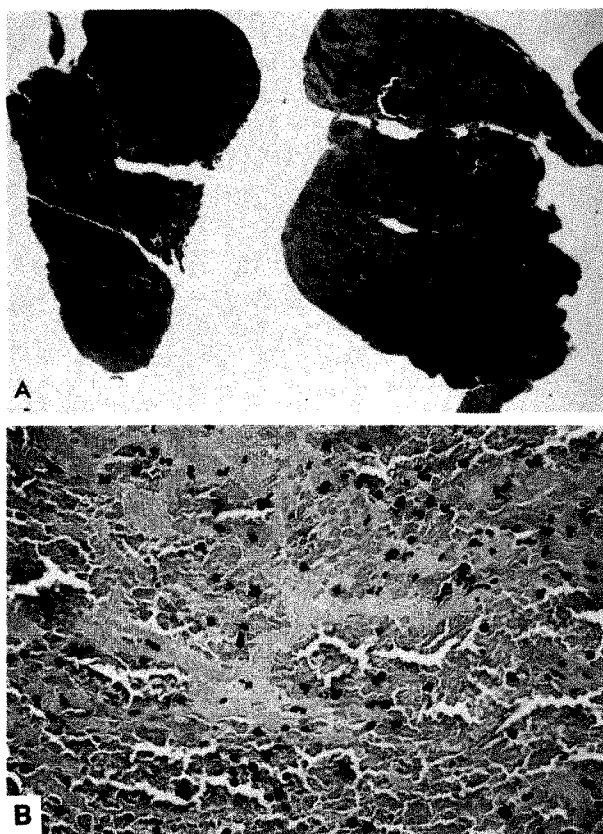
FIGURE 4. Photomicrographs of aspiration thrombectomy specimen from proximal right coronary artery (patient 1). *A*, low-power view of specimens (hematoxylin-eosin; original magnification ×36, reduced by 46%); *B*, high-power view shows composition of red blood cells, platelets and a few leukocytes (red thrombus) (hematoxylin-eosin; original magnification ×360, reduced by 46%).

In our small series of 8 patients, thrombectomy alone resulted in restoration of flow in 50%. Despite removal of thrombus material, it is likely that some residual thrombus remained at the lesion site and was undetectable angiographically. However, there is some theoretical benefit in decreasing the amount of thrombus at the PTCA site, especially as it relates to increased risk of reocclusion. It appears that the procedure is most likely to succeed with acute occlusion due to fresh thrombus, although the 1 patient had successful thrombectomy 6 days after occlusion.

In other cases reported,[4-10] a guiding catheter (8 or 9Fr) was used to aspirate thrombus material. Although this approach is suitable for proximal occlusions, distal thrombus cannot often be reached, and there is the risk of trauma to the proximal vessel. Use of the teleguide and steerable guidewire allows more distal obstruction to be approached with this technique and decreases the risk of vessel damage.

Analysis of aspirated thrombus material could be useful from a research standpoint. Histologic examination (Figure 4) could differentiate between red and white (platelet rich) thrombus; the latter may be more resistant to exogenous or endogenous thrombolysis, because of a lower fibrin content. Furthermore, with the ability to quantitate biochemical factors, such as thrombus concentration of plasminogen activator inhibitor-I, further insight into thrombus formation, propagation and resistance to lysis may be achieved.

Limitations of our study include the small number of patients, the retrospective design, and the absence of a control group for comparison of acute treatment results, including thrombolysis or PTCA alone. Furthermore, all patients did not undergo predischarge angiography to confirm the persistent patency of the dilated artery. Therefore, the definitive value of thrombectomy cannot be established from our study, because PTCA was successful and generally uncomplicated in patients with and without successful thrombus aspiration. Whether the theoretical benefits of thrombus removal before PTCA will translate into a clinically significant improvement in PTCA results is, therefore, not established. However, given the absence of observed complications from this technique, it appears reasonable to closely monitor results of its selective use in larger numbers of patients.

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Disparate Serum Lipid Changes Between Normotensive and Hypertensive Women During the Menstrual Cycle

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The homeostasis of serum lipids is dependent on a number of regulatory mechanisms, and in women, sex hormones have a major role.[1] The effect of the hormonal control of lipid metabolism in fertile normotensive women has been reported in a small number of studies.[2] Hypertensive women are at high risk for coronary artery disease, because of elevated blood pressure.[3] However, lipid changes occurring during the menstrual cycle in hypertensive women have not been studied. In the present study, serum lipids and lipoproteins were measured in the 3 phases of the menstrual cycle in hypertensive women and were compared with similar lipid profiles obtained in normotensive control subjects, in relation to hormonal changes.

We studied 40 untreated women with essential hypertension and 30 age-matched normotensive control subjects (Table I). Both groups had similar body mass index and incidence of smoking (p = not significant [NS]). No subject was diabetic, nor received any medication for 6 months before the study. All women had regular menstrual cycles ≥3 months before the study. During the study month, subjects were given a constant diet with regard to total calories, percentage of proteins, carbohydrates and lipids, saturated/unsaturated fatty acids ratio, and daily cholesterol, sodium and water intake. Hypertensive subjects had menstrual cycles ranging from 25 to 30 days, and controls from 26 to 30 days. Follicular, ovulatory and luteal phases were determined in all subjects. The ovulatory phase was defined using the Organon LH-color, an immunochemical test developed for demonstrating luteinizing hormone concentration in the urine of >50 IU/liter.[4] The follicular phase occurred on the fifth day of the cycle, and the luteal phase occurred 7 to 8 days after ovulation. Lipid profile measurements were obtained in all 3 phases of the menstrual cycle, and included total cholesterol, triglycerides, high- and low-density lipoprotein (HDL and LDL, respectively) cholesterol, and apolipoprotein (Apo) A_1 and ApoB (in mg/dl), and total/HDL cholesterol, ApoB/A_1 and LDL/ApoB ratios were calculated. At the same times, estradiol (in pg/ml), 17-OH-progesterone (in ng/ml) and free testosterone (in ng/dl) were also measured.

Serum cholesterol and triglycerides were assayed by enzymatic methods[5,6] (Abbot-Vision). HDL was measured after initial precipitation of chylomicrons and other lipoproteins, followed by enzymatic analysis of cholesterol[7] (Ames, SERA-PAK). LDL was calculated by the Friedewald formula (LDL = total cholesterol − HDL − triglycerides/5). ApoA$_1$ and B concentrations

were measured by immunonephelometric assay.[8] Estradiol-17 β and testosterone were determined using radioimmunoassay kits from Sorin Biomedical[9] (Italy), and 17-a-hydroxyprogesteron was determined using a radioimmunoassay kit from CIS Biointernational (France).[10]

To confirm presence or absence of arterial hypertension[11] in the 2 groups, ambulatory 24-hour blood pressure monitoring was performed in all subjects during the 3 phases of the menstrual cycle using Spacelabs-90207 equipment.

In all parameters of the lipid profile, mean values ± SD were calculated for the 3 phases of the menstrual cycle, and percent changes were computed. To evaluate within-group differences, the Student's paired t test was used and for between-group differences, the unpaired t test was used. A p value <0.05 was considered significant.

Of the sex hormones, estradiol and progesterone had similar values in the 2 groups in all 3 phases of the menstrual cycle, with normal cyclical pattern (Table II). Testosterone was higher in hypertensive subjects during the follicular (p = 0.02), ovulatory (p = 0.0001) and luteal (p = 0.000004) phases.

In hypertensive women, total cholesterol had higher concentrations at the follicular phase, and decreased progressively at the ovulatory and luteal (p = 0.02) phases (Table III). Throughout the menstrual cycle, total cholesterol was higher in hypertensive women, although the difference was not significant. Triglycerides had higher values in hypertensive than control subjects in all 3 phases of the menstrual cycle (p = 0.003, 0.05 and 0.007, respectively), but did not vary within groups (p = NS). HDL had lower values in hypertensive subjects, especially at the follicular (p = 0.0005), less at the ovulatory (p = 0.003), and minimal at the luteal (p = NS) phases. Thus, HDL in hypertensive subjects increased by 9% in the luteal phase, whereas it decreased in control by 3% (p = 0.0009). LDL tended to be higher in hypertensive subjects, decreasing progressively at ovulation (p = 0.05) and at the luteal phase (p = 0.0003), whereas in normotensives, the lowest values were at ovu-

TABLE I Patient Characteristics

	Control Subjects (n = 30)	Patients (n = 40)
Age (yr)	39.9 ± 4.3	40.7 ± 3.6
Body mass index (kg/m²)	24.6 ± 2.8	26.1 ± 4.0
Menstrual cycle (days)	27.8 ± 1.0	27.2 ± 1.5
Smokers (%)	10 (33.3)	18 (45.0)
24-hour mean systolic BP (mm Hg)	116 ± 6	137 ± 9
24-hour mean diastolic BP (mm Hg)	75 ± 4	91 ± 6

BP = blood pressure.

TABLE II Sex Hormone Values and Percent Change in the Three Phases of the Menstrual Cycle in the Two Groups (mean ± 1 SD)

	Values			Percent Change		
	Follicular Phase	Ovulation	Luteal Phase	Follicular Versus Ovulation	Follicular Versus Luteal	Ovulation Versus Luteal
Control subjects						
Estradiol (pg/ml)	85 ± 38	207 ± 109	126 ± 50	183 ± 170*	84 ± 116†	−30 ± 36*
Progesterone (ng/ml)	0.81 ± 0.41	1.43 ± 0.83	2.54 ± 1.28	109 ± 148‡	281 ± 291	107 ± 135‡
Testosterone (ng/dl)	0.31 ± 0.15	0.33 ± 0.18	0.29 ± 0.17	12 ± 48	−2 ± 54	−10 ± 36
Patients						
Estradiol (pg/ml)	81 ± 37	211 ± 101	138 ± 67	194 ± 154*	83 ± 83*	−22 ± 52*
Progesterone (ng/ml)	0.79 ± 0.44	1.71 ± 1.54	3.00 ± 2.32	156 ± 285‡	533 ± 789*	296 ± 394
Testosterone (ng/dl)	0.41 ± 0.18	0.53 ± 0.22	0.55 ± 0.25	37 ± 58*	45 ± 75‡	14 ± 54

*$p < 0.0001$; †$p < 0.005$; ‡$p < 0.0005$.

TABLE III Lipid Profile Values and Percent Change in the Three Phases of the Menstrual Cycle in the Two Groups (mean ± 1 SD) (mg/dl)

	Values			Percent Change		
	Follicular Phase	Ovulation	Luteal Phase	Follicular Versus Ovulation	Follicular Versus Luteal	Ovulation Versus Luteal
Control Subjects						
Total cholesterol	200 ± 31	207 ± 29	205 ± 32	1 ± 9	0 ± 10	0 ± 11
Triglycerides	69 ± 32	74 ± 34	71 ± 31	17 ± 60	12 ± 54	4 ± 35
LDL	137 ± 30	134 ± 27	138 ± 30	−1 ± 14	1 ± 15	4 ± 19
HDL	55.0 ± 11.6	57.6 ± 11.0	53.1 ± 13.0	6 ± 14	−3 ± 14	−8 ± 13*
Total/HDL cholesterol	3.91 ± 1.00	3.70 ± 0.85	4.09 ± 1.24	−4 ± 15	5 ± 17	11 ± 22*
ApoA₁	144 ± 27	148 ± 22	133 ± 23	5 ± 17	−6 ± 16*	−9 ± 15†
ApoB	108 ± 25	99 ± 22	101 ± 21	−5 ± 22*	−2 ± 25	6 ± 28
ApoA₁/B	0.77 ± 0.20	0.69 ± 0.17	0.79 ± 0.25	−8 ± 23*	5 ± 25	18 ± 32*
LDL/ApoB	1.32 ± 0.31	1.39 ± 0.29	1.38 ± 0.27	9 ± 28	9 ± 27	3 ± 27
Patients						
Total cholesterol	218 ± 39	214 ± 41	208 ± 41	−2 ± 11	−4 ± 11*	−2 ± 10
Triglycerides	107 ± 65	100 ± 69	104 ± 62	−2 ± 36	5 ± 43	11 ± 35
LDL	152 ± 35	144 ± 40	138 ± 37	−5 ± 17*	−9 ± 15‡	−3 ± 19
HDL	45.1 ± 9.4	49.6 ± 9.5	49.8 ± 10.8	13 ± 24†	13 ± 23†	1 ± 16
Total/HDL cholesterol	5.05 ± 1.35	4.45 ± 1.17	4.36 ± 1.21	−10 ± 17†	−12 ± 20‡	0 ± 26
ApoA₁	136 ± 32	144 ± 31	139 ± 32	8 ± 23	4 ± 19	−2 ± 16
ApoB	115 ± 35	110 ± 37	117 ± 38	−1 ± 35	4 ± 25	14 ± 41
ApoA₁/B	0.87 ± 0.29	0.79 ± 0.30	0.88 ± 0.33	−6 ± 37	3 ± 29	18 ± 43
LDL/ApoB	1.38 ± 0.31	1.37 ± 0.33	1.23 ± 0.31	3 ± 28	−8 ± 23*	−7 ± 30*

*$p < 0.005$; †$p < 0.0005$; ‡$p < 0.0001$.
Apo = apolipoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

lation ($p = 0.01$). The total/HDL cholesterol ratio had higher values in hypertensive subjects, mostly at the follicular phase ($p = 0.0002$); it decreased at ovulation ($p = 0.004$) and reached the values of the controls at the luteal phase ($p = NS$). In contrast, total/HDL cholesterol ratio in normotensive women decreased at ovulation and increased at the luteal phase ($p = NS$). Thus, total/HDL cholesterol ratio decreased from the follicular to the ovulatory phase by 12% in hypertensive subjects, whereas it increased by 5% in controls ($p = 0.0005$).

All concentrations of ApoB were higher in hypertensive women, whereas they decreased in normotensives at the ovulatory ($p = 0.05$) and less at the luteal ($p = NS$) phase, with no between-group differences. The ApoB/A₁ ratio decreased significantly at the ovulatory phase in control subjects and increased again at the luteal phase ($p = 0.009$), whereas no significant changes were observed, and no differences between groups were documented in hypertensives. The LDL/ApoB ratio retained uniformity during the menstrual cycle in control subjects, whereas it decreased at the luteal phase in hypertensives ($p = 0.01$).

The incidence of cardiovascular disease is higher in men at any level of risk factors,[12] whereas premenopausal women appear to be practically immune to coronary artery disease. Whether the occurrence of natural or surgical menopause alters the risk of coronary artery disease remains controversial,[13] although many studies reported an increase in coronary artery disease after menopause.[14,15] Sex differences in lipid profile are apparent from birth, when female cholesterol levels are higher than are male levels,[16] whereas in the fertile adult life, normotensive women have lower total cholesterol and LDL fraction.[1] Furthermore, HDL is higher in women regardless of age.[12,15]

Previous studies also reported fluctuations in total cholesterol and lipoprotein subfractions during the men-

strual cycle of normotensive women.[2] Our data show that hypertensive women have higher triglycerides values. This may be secondary to insulin resistance and hyperinsulinemia, reported in untreated hypertensive subjects.[17] However, total cholesterol decreased slightly in midcycle, and more in the luteal phase in hypertensive subjects. Our results agree with those reported by Barclay et al[18] concerning normotensive women, whereas Adlercreutz and Tallqvist[19] observed a second increase in total cholesterol in the late luteal phase in normotensive women only.

The present study also shows a cyclic change in LDL, as well as ApoB, in the menstrual cycle of hypertensive and normotensive women. In hypertensive subjects, LDL was decreased at ovulation and even more at the luteal phase, whereas in normotensives, it decreased in midcycle and increased at the luteal phase. The reduction in total cholesterol and LDL at ovulation may follow the peak increase in plasma 17-b-estradiol, which occurs before ovulation. The delay between the achievement of peak plasma estradiol concentrations and the decrease in cholesterol may reflect dissimilar variations in plasma half-life of LDL and ApoB. Thus, it appears that LDL in hypertensive subjects may have a decreased availability to peripheral tissues during the luteal phase, with obvious clinical significance.

In our study we detected that hypertensive women have higher (but not abnormal) values of testosterone. This may help to explain the lower values of HDL observed in hypertensive subjects, and the decrease at the luteal phase, when testosterone has the highest concentrations. It is established from previous studies that androgens decrease HDL in men, increasing the activity of hepatic lipase that provokes a reduction in the HDL_2 subfraction. In both groups, HDL and its major protein carrier $ApoA_1$ increased at the ovulatory phase (moderately in normotensive women and significantly in hypertensives). However, hypertensive subjects had lower HDL than did normotensives, especially at the follicular phase ($p = 0.0005$), and the difference between the 2 groups was minimized at the luteal phase ($p = NS$). The role of increased testosterone levels at the luteal phase of hypertensive subjects is unclear concerning HDL variations.

This higher level of HDL in normotensive women increases resistance to coronary artery disease, whereas relatively low HDL values add another risk factor to hypertensives. Kim and Kalkhoff[2] reported similar results concerning HDL and $ApoA_1$ in normotensive women only. The total/HDL cholesterol ratio (the most indicative coronary artery disease marker) was reduced at ovulation in both groups examined; at the luteal phase, it

increased again in normotensive subjects, whereas it was further decreased in hypertensives. Thus, hypertensive subjects are not continuously burdened with dislipidemia, with obvious clinical effects. This may be due to altered hormonal lipid effects in hypertensive subjects who have persistently increased testosterone levels.

It is concluded that serum lipid and Apo variations during the menstrual cycle differ significantly between hypertensive and normotensive women. This should be taken under consideration in the overall treatment of patients with the added risk factor of hypertension.

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Atrial and Ventricular Approaches for Radiofrequency Catheter Ablation of Left-Sided Accessory Pathways

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Radiofrequency ablation has been very successful in the treatment of Wolff-Parkinson-White syndrome.[1-4] Two approaches for left-sided pathways have been described. The retrograde aortic approach involves arterial puncture and advancement of the catheter under the mitral leaflet to the ventricular aspect of the annulus. The transseptal approach consists of crossing the atrial septum with a luminal catheter through which the ablation catheter reaches the atrial aspect of the mitral annulus. The proponents of each approach have reported excellent success.[1,2] The present report describes experiences with each approach performed in 1 laboratory.

All patients with left free wall accessory pathways undergoing radiofrequency ablation at our hospital between October 1990 and November 1991 were included in this study. The strategy in the first period (to June 1991) was to give priority to the retrograde aortic approach and crossover to the transseptal approach in selected cases. In the second period the method of choice was the transseptal approach, with fallback to the retrograde aortic approach.

The electrophysiology study was performed after patients gave written and verbal informed consent. Programmed stimulation was performed as previously described[5] to confirm accessory pathway participation in the clinical tachycardia and to localize the accessory pathway. Ablation followed the diagnostic study. Programmed stimulation was repeated 30 to 45 minutes after successful ablation. All patients received a 10,000 U bolus of heparin intravenously on instrumentation of the left heart, with fentanyl and midazolam given for sedation. A 7Fr catheter with a 4 mm tip electrode was used for ablation (Mansfield-Webster, Watertown, Massachusetts). For the retrograde aortic approach, the ablation catheter was inserted in the femoral artery, advanced into the left ventricle across the aortic valve and positioned under the mitral leaflet at the annulus. With this technique, ablation was performed from the ventricular aspect of the mitral valve annulus.[1,3-4] For the transseptal approach, an 8Fr Mullins sheath was advanced in the left atrium through the atrial septum.[6,7] The ablation catheter was advanced through the sheath and positioned at the mitral annulus. A suitable site for ablation was identified during anterograde conduction using ≥1 of the following criteria: (1) presence of both atrial and ventricular electrograms; (2) presence of an accessory pathway potential; (3) early ventricular activation with the intrinsic deflection of the ventricular electrogram preceding the delta wave; or (4) a QS pattern on the unipolar ventricular electrogram. Similarly,

during reentrant tachycardia or ventricular pacing, the following criteria were used for determining the optimal site for ablation: (1) presence of both atrial and ventricular electrogram; (2) presence of an accessory pathway potential between the ventricular and atrial electrogram; or (3) earliest atrial activation during tachycardia or ventricular pacing.

A bipolar electrogram (filtered at 40 to 400 Hz) was recorded from the distal pair of the ablation catheter, in addition to a unipolar electrogram from the distal electrode (0.5 to 400 Hz). Radiofrequency current (400 to 600 ma) was delivered between the 4 mm electrode and a back plate, using a Radionics RFG-3C generator (Radionics Inc., Burlington, Massachusetts) that allows continuous measurements of current, voltage, power and impedance. Current delivery was discontinued if unsuccessful within 10 seconds or if impedance increased. Success rate, fluoroscopy time and number of attempts were compared. All patients were followed clinically and electrocardiographically, and 15 consented to repeat electrophysiology study at 3 months. Values were expressed as mean ± SD. Student's t test for unpaired data, and chi-square test were used for statistical analysis. A p value <0.05 was considered significant.

Ablation was performed in 80 patients, with 82 left lateral accessory pathways associated with symptomatic supraventricular tachycardia. Forty-nine patients (31 men and 18 women, mean age 33 ± 16 years) underwent the retrograde aortic approach, and 31 (17 men and 14 women, mean age 32 ± 15) underwent the transseptal approach. The retrograde aortic approach was successful in 43 of 49 patients (88%), whereas the transseptal approach was successful in 31 of 31 (100%) (p <0.03). In 3 patients, the transseptal technique was successful after the retrograde aortic approach was unsuccessful. It was not necessary to switch from the transseptal to the retrograde aortic approach to achieve successful ablation. All but 1 patient receiving the retrograde aortic approach were ablated from the ventricular side (Figure 1). In 1 patient, ablation was achieved from the atrial site. In patients undergoing the transseptal technique, ablation was achieved from the atrial side (Figure 2) in all but 1 whose accessory pathway was anterolateral. It was difficult to obtain a stable catheter position on the atrial aspect of the annulus at that site. In this patient, ablation was obtained with the transseptal approach from the ventricular side. The mean fluoroscopy time was not different for the 2 approaches (34 ± 18 minutes for transseptal, and 42 ± 29 for retrograde aortic). The mean number of attempts for each approach did not differ (5.9 ± 4.2 for transseptal, and 7.3 ± 0.6 for aortic; Table I). In the transseptal group, 1 patient had asymptomatic intermittent preexcitation without tachycardia at 3-month follow-up. No other recurrences were observed in the transseptal group after a mean follow-up of

4 ± 2.2 months. In the retrograde aortic group, 2 patients had recurrence of accessory pathway conduction and tachycardia 2 months after ablation. Both patients had intermittent preexcitation 24 hours after the procedure, with no inducible tachycardia. Another patient had recurrence of preexcitation after 3 months, but no retrograde and poor anterograde conduction over the accessory pathway. All other patients having the retrograde aortic approach were free of arrhythmias with no preexcitation after a mean follow-up of 9 ± 2.7 months. No complications were observed in the transseptal group.

TABLE I Radiofrequency Ablation of Left Lateral Accessory Pathways with Transseptal and Transaortic Approaches

	Success Rate	Fluoro Time (min)	No. of Attempts	Follow-Up (mos)
Transaortic (n = 49)	88%	42 ± 29	7.3 ± 7.6	9 ± 2.7
Transseptal (n = 31)	100%	34 ± 18	5.9 ± 4.2	4 ± 2.2
p value	0.03	NS	NS	0.0001

Fluoro = fluoroscopy; NS = not significant.

FIGURE 1. Radiofrequency ablation of left lateral accessory pathway using retrograde aortic approach. *A*, recording before ablation from ablation catheter shows small atrial (A) and large ventricular (V) electrogram with rapid intrinsic deflection. Ventricular electrogram precedes onset of δ wave indicating proximity to accessory pathway. *B*, radiofrequency energy *(arrow)* eliminates preexcitation within 2 cycles *(asterisk)*. Ab_b = bipolar recording on ablation catheter; Ab_u = unipolar recording on ablation catheter; CSd = coronary sinus distal; CSp = coronary sinus proximal.

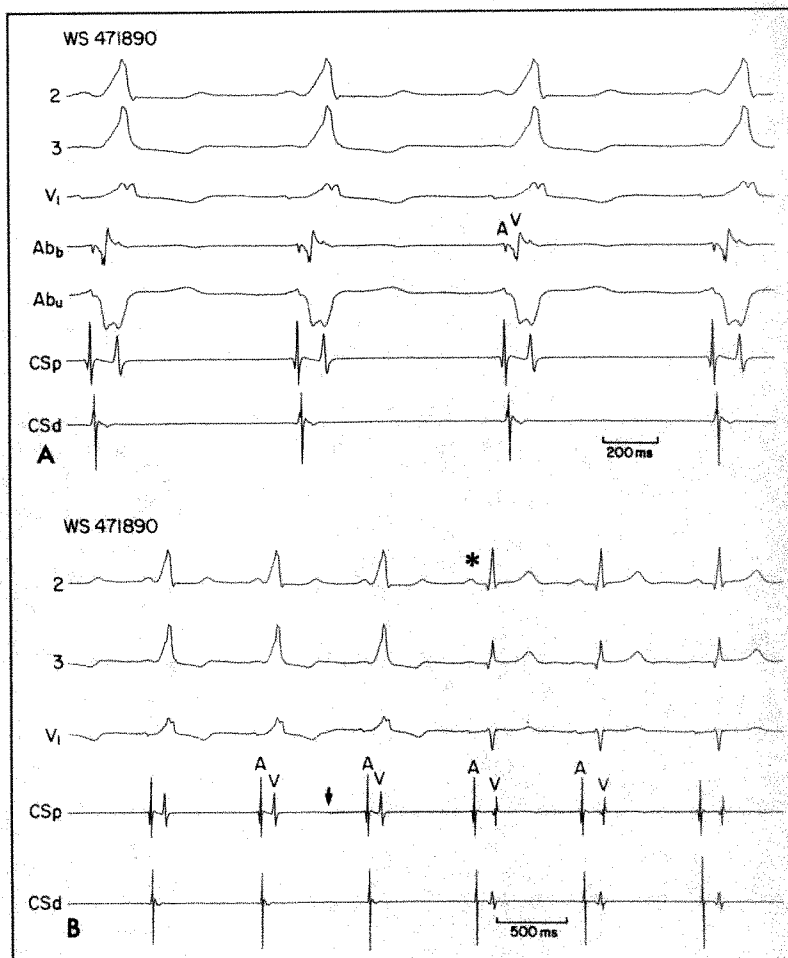FIGURE 2. Radiofrequency ablation on atrial aspect of mitral annulus using transseptal technique. Recording before ablation showed prominent atrial (A) and ventricular (V) electrogram. Absence of isoelectric segment between atrial and ventricular electrogram indicates proximity to accessory pathway. Radiofrequency energy eliminated preexcitation within 2 cycles (not shown). Abbreviations as in Figure 1.
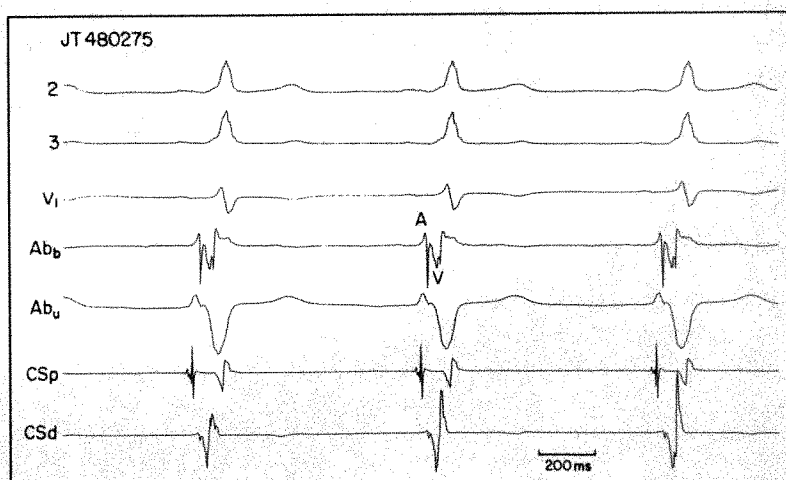
All patients tolerated the procedure well, with minimal discomfort. In the retrograde aortic group, 1 patient had a large hematoma at the site of the arterial puncture, and another had ventricular fibrillation related to a sudden impedance increase during the successful radiofrequency ablation attempt. After ablation, patients were treated with aspirin (325 mg/day for 1 month).

Radiofrequency ablation of left free wall accessory pathways using either a retrograde aortic or transseptal approach has been very effective. Using a conservative approach generally limiting fluoroscopy time to 60 minutes, the transseptal approach provided a slightly better success rate than did the retrograde aortic approach. Mean fluoroscopy time and number of attempts necessary to achieve successful ablation did not differ. Furthermore, 2 clinical recurrences of tachycardia were observed with the aortic approach, whereas no recurrences were observed in the transseptal group. We conclude that both techniques are comparable, and choice depends on operator preference and experience. With the retrograde aortic approach, the ablation catheter is placed beneath the mitral valve leaflet on the ventricular aspect of the annulus, and the recorded electrogram is mainly characterized by a small atrial and a large ventricular electrogram (Figure 1).[1,3-4] The atrial electrogram and the pathway potential may be difficult to see during ventricular pacing or reentrant tachycardia, as required for concealed pathways. It is also technically more difficult to map the subvalvular region in a systematic way, and some locations may be difficult to access. The atrial side of the annulus can be mapped with the retrograde aortic approach, but this is difficult, and catheter stability is a problem.

With the transseptal approach, the catheter is advanced to the atrial side of the mitral valve, and in general, good atrial and ventricular electrograms are seen (Figure 2).[2] It is much easier to see the atrial electrogram during ventricular pacing and reentrant tachycardia. Consequently, we prefer this approach for unidirectional retrograde pathways. Systematic mapping of the atrioventricular annulus is generally easier and faster with this approach. It can be difficult to maintain catheter stability for anterolateral pathways, where the catheter tends to fall into the left atrial appendage.

In conclusion, both the transseptal and aortic methods are comparable, and priority depends on operator preference. It is useful to be familiar with both techniques to allow an alternate approach in difficult cases.

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Doppler Detection of Valvular Regurgitation After Radiofrequency Ablation of Accessory Connections

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Radiofrequency current was used recently to ablate accessory connections in patients with supraventricular tachycardia.[1-5] After locating the accessory connection by electrophysiologic mapping, ablation is achieved by positioning a 7Fr catheter (with 4 mm electrode at distal tip) within the ipsilateral cardiac chamber and adjacent to the accessory connection. Radiofrequency current is then delivered at the point of earliest electrical activation along the atrioventricular valve annulus. For a left-sided accessory connection, the catheter is usually passed retrograde across the aortic valve into the left ventricle and under the posterior mitral valve leaflet. For a right-sided accessory connection, the catheter is passed anterograde into the right atrium or ventricle.[1-5] Systematic evaluation of the effects of this technique on the function of all cardiac valves has not been reported. This study evaluates the effects of catheter manipulation and radiofrequency current delivery on valve competence.

From May 1990 to December 1991, all patients undergoing radiofrequency ablation were examined prospectively with 2-dimensional, pulsed and color flow Doppler echocardiography. Echocardiograms were obtained within 1 week before and 1 week after the radiofrequency ablation procedure. Pulsed and color flow Doppler examinations of all 4 cardiac valves were performed from standard parasternal and apical views. The amount of valvular regurgitation was graded according to the following criteria: (1) mild = small, narrow jet of low amplitude detected near valve origin on color Doppler echocardiography, with confirmation by pulsed Doppler echocardiography and with normal cardiac chamber dimensions; (2) moderate = easily detected, high-amplitude jet associated with cardiac chamber enlargement; and (3) severe = wide, easily detected, high-amplitude jet with marked chamber enlargement.

During this period, 44 patients underwent 52 ablation procedures on 46 connections. Three patients (all with left-sided accessory connections) were excluded from the study because pre- and postablation echocardiographic examinations were not performed. The remaining 41

patients with 43 accessory connections (9 right, 28 left, 2 bilateral and 2 dual atrioventricular nodal) composed the study group. Patients ranged in age from 2 to 22 years (mean 12) and in weight from 16 to 98.5 kg (mean 50). Two patients had cardiac defects (1 Ebstein anomaly and 1 mitral valve prolapse).

Thirteen patients underwent ablation with the catheter at the tricuspid valve (9 right, 2 bilateral and 2 atrioventricular nodal). Current was delivered from the ventricular side of the valve annulus in 4 patients and from the atrial side in the remaining 9. Before ablation in this group, 13 patients had tricuspid regurgitation (12 mild and 1 moderate), 7 had mild pulmonic regurgitation, 4 had mild mitral regurgitation, and 1 had mild aortic regurgitation. On the postablation echocardiogram, no change in the presence or severity of regurgitation was seen for any valve.

Thirty patients underwent ablation with the catheter at the mitral valve (28 left and 2 bilateral). A retrograde aortic approach was used to deliver the current in all patients. Before ablation in this group, 22 patients had mild tricuspid regurgitation, 15 had mild pulmonic regurgitation, 6 had mild mitral regurgitation, and none had aortic regurgitation. On the postablation echocardiogram, no change in the amount of tricuspid or pulmonic regurgitation was found for any patient; however, 4 developed new mild mitral regurgitation (12% increase), and 9 developed new mild aortic regurgitation (30% increase). The development of aortic and mitral regurgitation was independent of age, weight and number of ablation attempts (using linear regression analysis, $p = 0.21$ to 0.32).

Radiofrequency ablation requires catheter manipulation across the aortic or tricuspid valve, or both, as well as delivery of a radiofrequency current to tissue near the mitral or tricuspid valve annular rings, or both.[1-5] In this study we detected a 12% increase in the incidence of mild mitral regurgitation when radiofrequency ablation was used for a left-sided accessory connection. We speculate that the new onset mitral regurgitation may result from catheter manipulation or direct tissue injury where radiofrequency current was used. A similar effect was not seen on the tricuspid valve in patients with right-sided pathways, possibly because only 4 of the 13 with right-sided connections underwent aggressive catheter manipulation

to deliver the radiofrequency current from the ventricular side of the tricuspid annulus. The remaining 9 patients received only catheter placement in the right atrium, and current delivery from the atrial side of the valve. Furthermore, the mitral valve with its 2 papillary muscles subjected to systemic pressures may be more vulnerable to damage and subsequent leakage than is the tricuspid valve with its multiple papillary muscles subjected only to normal pulmonary pressures.

We observed a 30% increase in the incidence of aortic regurgitation when radiofrequency ablation was used for a left-sided accessory connection. Vigorous manipulation of the ablation catheter to position the distal tip properly may directly damage the aortic valve leaflets. Furthermore, prolonged placement of the catheter across the active valve leaflets may cause stretching or compression of leaflet tissue, and subsequent valvular incompetence. This experience underscores the importance of minimizing manipulation of the ablation catheter across the aortic valve, and suggests that the transseptal approach should be considered if prompt catheter placement and ablation are not achieved.

Although long-term results are unknown, these findings of new onset mitral and aortic regurgitation warrant further investigation and follow-up studies. Regardless of the catheter approach used, the effects of radiofrequency ablation on valve competence can be readily examined with Doppler echocardiography. Therefore, we recommend that a Doppler echocardiogram be obtained in all patients who have undergone radiofrequency ablation of a left-sided accessory connection.

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Safety of Percutaneous Transvenous Balloon Mitral Commissurotomy in Patients with Mitral Stenosis and Thrombus in the Left Atrial Appendage

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Percutaneous transvenous mitral commissurotomy (PTMC) is an effective therapeutic alternative for patients with symptomatic mitral stenosis (MS).[1-4] Left

atrial thrombus occurs frequently in MS and is generally considered as a contraindication to PTMC.[1-4] Since the introduction of transesophageal echocardiography, even a small thrombus confined to the left atrial appendage can be detected.[5,6] Whether such patients should be denied the potential benefits of PTMC and be subjected to mitral valve surgery is an issue of clinical interest. To our knowledge, there have been few studies of PTMC in

patients with MS and left atrial thrombus.[6,7] This study reports on the safety and efficacy of PTMC in patients with MS and left atrial appendage thrombus.

We performed transthoracic and transesophageal echocardiographic examinations for all candidates of

FIGURE 1. Transesophageal echocardiography showing large left atrial thrombus (TH) *(arrow)* attached to left atrial posterior wall in patient *(A)*, and left atrial appendage (APP) thrombus with mobile part *(arrow)* extending into left atrial cavity in another patient *(B)*. Both cases were judged to be inappropriate for percutaneous transvenous mitral commissurotomy (PTMC). AO = aorta; LA = left atrium; RV = right ventricle; RVOT = right ventricular outflow tract.

PTMC. Of twenty-six cases with left atrial thrombi, 20 were considered inappropriate for PTMC, because the thrombi were large, mobile or present in the left atrial cavity (Figure 1). The other 6 cases had fixed thrombi with diameters <2.5 cm confined to the left atrial appendage (Figure 2). After giving informed consent, these 6 patients underwent PTMC. Inoue balloon catheter (Toray Industries, Japan) was chosen for PTMC, because it involves minimal manipulation in the left atrium.[1,3] The 6 patients included 5 women and 1 man (aged 41 to 55 years, mean 50 ± 5). The rhythms were atrial fibrillation in 4 cases, and sinus rhythm in 2. New York Heart Association functional class was III in 5 cases, and IV in 1. Immediately before and 1 week after PTMC, cardiac catheterization was performed to evaluate the changes in hemodynamic data, left ventriculography and aortography. Cardiac output was measured by the thermodilution method. Comprehensive echocardiographic examinations (including the transthoracic and transesophageal approach) were performed to assess Doppler-derived mitral valve area by the pressure half-time method and to detect complications related to the procedure. All patients underwent careful examinations to detect any evidence of systemic thromboembolism after PTMC. Data are expressed as mean ± SD. The paired Student's t test was used to assess the differences between pre- and post-PTMC data. A p value <0.05 was considered statistically significant.

After PTMC, patients had significant improvements in mean left atrial pressure, mitral pressure gradient, mitral valve area and cardiac output (Table I). At follow-up visits 2 to 3 weeks after the procedure, all cases had improvement in New York Heart Association functional class (class II in 5 cases, and class I in 1). There was no mortality, emergency surgery, cardiac tamponade nor systemic thromboembolism. Although the degree of mitral regurgitation was increased in 4 cases, the severity remained in Sellers' grade 1 or 2. Transesophageal echocardiography showed left-to-right shunt at
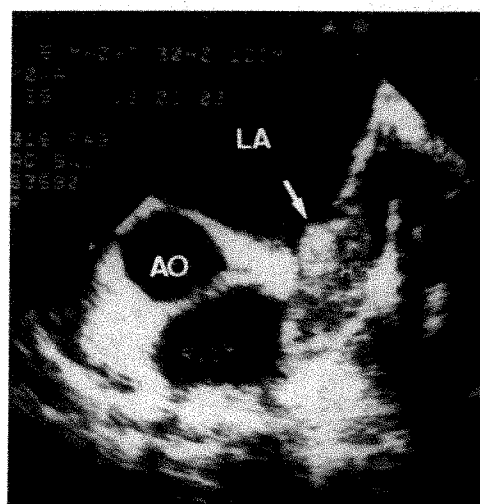
FIGURE 2. Transesophageal echocardiography showing small and fixed thrombus (TH) located at left atrial appendage. Patient underwent successful percutaneous transvenous mitral commissurotomy after giving informed consent. Other abbreviations as in Figure 1.

atrial level in all 6 cases; however, only 1 had significant oxygen step-up, with Qp/Qs = 1.4 during the cardiac catheterization study.

The efficacy of PTMC is well documented. However, it has some risks of complications.[2-4] Complications frequently reported include mortality, emergency surgery, cardiac tamponade, systemic thromboembolism, mitral regurgitation and atrial septal defect. The complication rates of systemic thromboembolism range from 0 to 4%.[2-4] Hence, left atrial thrombus was considered as an absolute contraindication for PTMC. However, all previous studies depend on transthoracic echocardiography to detect left atrial thrombus.[2-4] The diagnostic accuracy of transthoracic echocardiography to detect left atrial thrombus is not satisfactory.[5,6] Because transesophageal echocardiography improves the diagnostic sensitivity of left atrial thrombus, more patients with MS would be found to have left atrial thrombus. The issue of whether patients with small and fixed thrombus confined to the left atrial appendage should be denied the potential benefits of PTMC is worth examining. Our preliminary experience may shed some light on this crucial point. All 6 cases in this series had successful PTMC without clinically evident thromboembolic complication.

PTMC with the Inoue balloon catheter has lower thromboembolic rates (0% to 1.4%) than do other balloon catheters (3 to 4%) in the literature.[2-4] The special character of the Inoue balloon catheter may explain the lower rates of thromboembolic complication. First, its coiled left atrial guidewire can prevent the catheter from entering the left atrial appendage (the most frequent location of thrombus). Second, its flow-directed passage from the left atrium to left ventricle can minimize manipulation of the catheter in the left atrium.

From our experience, thrombus in the left atrial appendage is not an absolute contraindication for PTMC. In selected patients with MS who have small and fixed left atrial appendage thrombus, PTMC could be carefully performed with the Inoue balloon catheter with acceptably low complication risks.

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The Four Subtypes of Anomalous Origin of the Left Main Coronary Artery from the Right Aortic Sinus (or from the Right Coronary Artery)

William C. Roberts, MD, and Jamshid Shirani, MD

Most published reports of coronary arterial anomalies concern a single patient or only a small group of patients. Although much good and useful information, of course, can be derived from the study of a single patient, multiple cases of a major coronary anomaly are required to observe the various subgroups of a single major anomaly. We have studied at necropsy 17 patients in whom the left main coronary artery (LMCA) arose from either the right aortic sinus or the most proximal portion of the right coronary artery.[1-5] After its origin, the LMCA coursed to the left side of the heart by 1 of 4 routes, and the clinical consequences of such courses are described in this report.

Pertinent clinical and necropsy findings in the 17 patients are summarized in Table I, and the 4 subtypes are illustrated in Figure 1. In 2 patients (12%) (cases 1 and 2 [Table I]), the anomalously arising LMCA coursed anterior (group A) to the right ventricular outflow tract to reach the anterior sulcus (the anterior portion of the heart immediately anterior to the ventricular septum), where it then divided into the left anterior de-

scending and left circumflex coronary arteries.[5] In neither patient did the coronary anomaly appear to have caused cardiac dysfunction or myocardial ischemia.

In 9 patients (53%) (cases 3 to 11), the anomalously arising LMCA coursed in between (group B) the ascending aorta and pulmonary trunk before reaching the anterior sulcus.[2-4] The ostium of the LMCA was slit-like in 8 patients. In 7 of the 9 patients death was attributed to the coronary anomaly: sudden outside the hospital in 6, and secondary to severe intractable congestive heart failure (the result of a previous large acute myocardial infarct that had healed) in 1 (case 9).

In 2 patients (12%) (cases 12 and 13), the anomalous LMCA coursed within the crista supraventricularis muscle (group C) behind the right ventricular outflow cavity before reaching the anterior sulcus, and then dividing into the left anterior descending and left circumflex coronary arteries.[1] Neither patient ever had evidence of myocardial ischemia or cardiac dysfunction.

In 4 patients (23%) (cases 14 to 17), the anomalous LMCA coursed dorsal (group D) to the ascending aorta before reaching the usual area of bifurcation into the left anterior descending and left circumflex coronary arteries.[5,6] Although 2 of the 4 patients died from cardiovas-

TABLE I Clinical and Morphologic Findings in 17 Patients with Anomalous Origin of the Left Main Coronary Artery from the Right Coronary Artery or the Right Aortic Sinus

Case	Age (yr) & Sex	Origin of LMCA	Anomaly Group*	Length of LMCA (cm)	AP	SD	Death Outside Hospital	Cause of Death	Length of RCA > LCCA	Slit-Like Ostium	No. of Major CAs >75% ↓ in CSA by Plaque	LV Scar (1 to 3+)	HW (g)
1	22 M	RAS	A	4.5	0	+	+	HC	+	0	0	0	870
2	44 F	RAS†	A	3.0	+	+	+	Trauma	+	0	0	0	255
3	13 F	RAS	B	1.1	0	+	+	Coronary anomaly	+	+	0	0	210
4	14 M	RAS	B	1.2	0	+	+	Coronary anomaly	+	+	0	0	370
5	14 M	RAS	B	—	0	+	+	Coronary anomaly	—	+	0	0	380
6	19 M	RAS	B	1.1	0	+	+	Coronary anomaly	+	+	0	0	325
7	29 M	RAS	B	—	+	+	+	Coronary anomaly	0	+	0	+	350
8	39 F	RAS	B	—	0	+	+	Coronary anomaly	0	+	0	0	220
9	64 F	RAS	B	2.4	+	0	0	Coronary anomaly	+	+	0	+++	510
10	81 M	RAS	B	2.0	0	+	+	Trauma	+	0	0	0	420
11	50 F	RAS†	B	—	0	+	+	Atherosclerotic CAD	+	0	3	+++	650
12	34 M	RAS	C	4.7	0	0	+	Trauma	+	0	0	0	330
13	48 M	RAS	C	4.5	0	+	+	Trauma	+	0	0	0	550
14	32 M	RAS	D	3.3	0	+	+	Trauma	0	0	0	0	325
15	45 M	RAS	D	4.5	+	+	+	Atherosclerotic CAD	+	0	1	+++	580
16	57 F	RAS	D	3.6	0	0	+	Opiate addiction‡	+	0	0	0	300
17	69 M	RCA	D	3.0	0	0	0	Forme fruste Marfan	+	0	0	0	685

*See Figure 1 for description.
†Common ostium of both RCA and LMCA.
‡Complications arising from the addiction.
AP = angina pectoris; CA = coronary artery; CAD = coronary artery disease; CSA = cross-sectional area; HC = hypertrophic cardiomyopathy; HW = heart weight; LCCA = left circumflex coronary artery; LMCA = left main coronary artery; LV = left ventricular; RAS = right aortic sinus; RCA = right coronary artery; SD = sudden death; + = present or positive; 0 = absent or negative; —— = no information available.
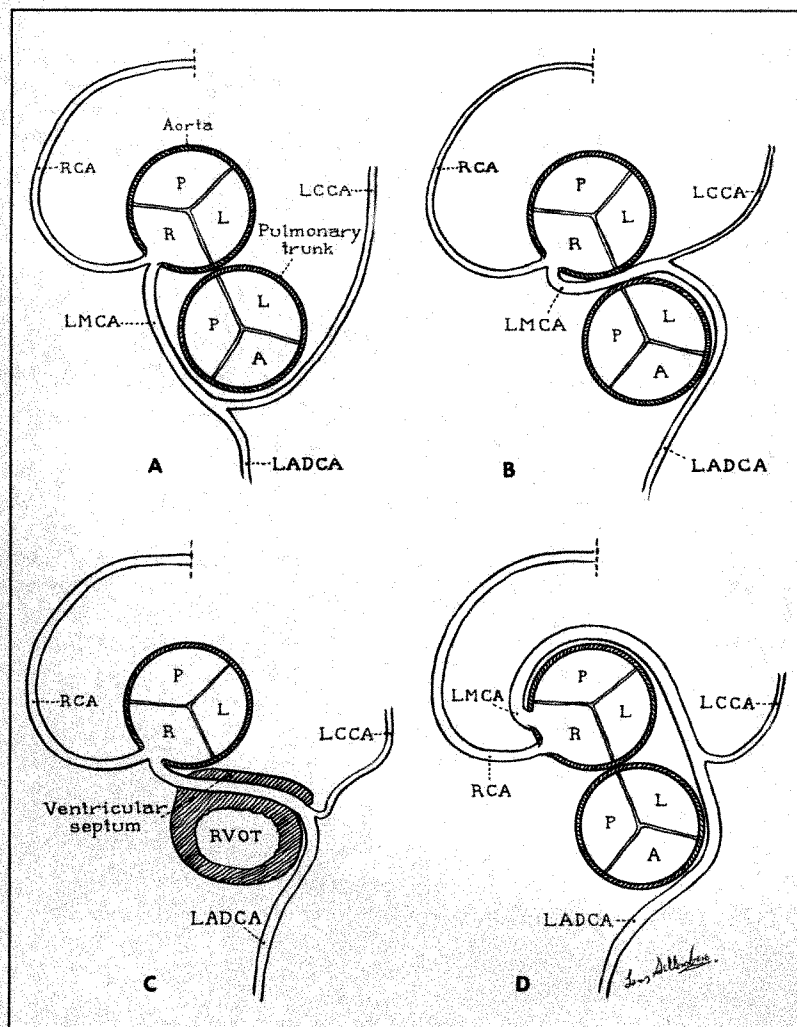
FIGURE 1. Diagram showing the 4 subtypes of anomalous origin of the left main coronary artery (LMCA) from the right aortic sinus. A = anterior; L = left; LADCA = left anterior descending coronary artery; LCCA = left circumflex coronary artery; P = posterior; R = right; RCA = right coronary artery; RVOT = right ventricular outflow tract.

cular disease (atherosclerosis in 1, and Marfan-type aortic disease in the other), in none could the cardiac problems be attributed to the coronary anomaly.

This brief report indicates that if an anomalously arising LMCA courses anterior (group A) to the right ventricular outflow tract, behind the right ventricular outflow tract (infracristal) (group C) or dorsal (group D) to the ascending aorta, symptoms of cardiac dysfunction or myocardial ischemia do not result. In contrast, if the anomalously arising LMCA courses between (group B) the pulmonary trunk and ascending aorta, symptoms of myocardial ischemia usually occur, and death is a frequent consequence.

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Congenital Hypoplasia of Both Right and Left Circumflex Coronary Arteries

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When the right coronary artery is dominant, i.e., it courses to the crux of the heart, the left circumflex coronary artery is usually quite small and therefore may

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be considered hypoplastic (Figure 1). Conversely, when the left circumflex is the dominant coronary artery, i.e., it courses to the crux of the heart, the right coronary artery is usually small and therefore may be considered hypoplastic (Figure 1). Hypoplasia of both right and left circumflex coronary arteries in the same heart, however, is a rare occurrence (Figure 1). Examination of 3,400 hearts during the last 8 years disclosed at least 8 to have hypo-
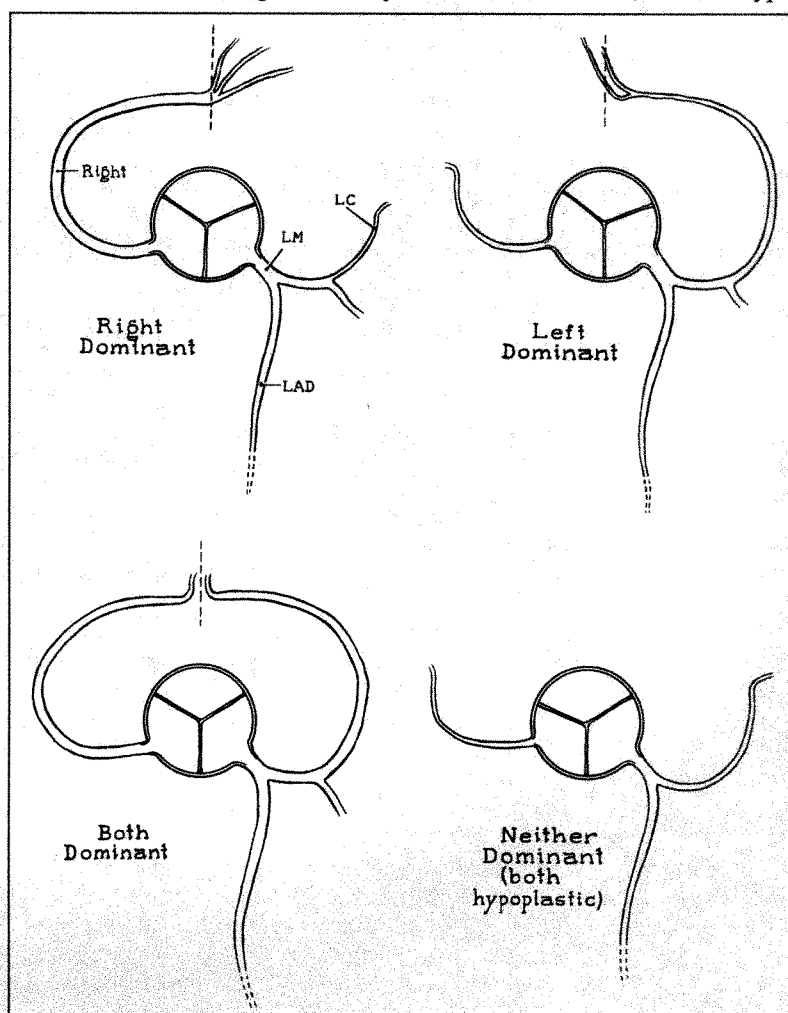
FIGURE 1. Diagram showing graphic definitions of *dominance* and *hypoplasia*. The 8 patients described had right and left circumflex (LC) coronary arteries similar to those depicted in the *bottom right diagram*. LAD = left anterior descending; LM = left main coronary artery.

TABLE I Clinical and Necropsy Findings in Eight Patients with Hypoplastic Right and Left Circumflex Coronary Arteries

Pt.	Necropsy Number	Age (yr)	Race	Sex	SD	SH	A	Associated Disorders	HW (g)	Number of CAs >75% ↓ in CSA	LV N	LV F	LADCA Past Apex (cm)	Actual Length/ Potential Length (cm) RCA	LCCA
1	DCMEO# 87-05-400	26	B	M	+	0	+	Stenotic unicuspid aortic valve	760	0	0	0	+(5)	6/12	9/12
2	DCMEO# 83-01-004	33	B	M	+	+	+	0	565	0	0	0	+(3)	9/12	7/12
3	DCMEO# 87-06-528	35	B	M	+	0	0	WPW syndrome	420	0	0	0	+(2)	7/11	9/12
4	DCMEO# 87-09-868	35	B	M	+	+	+	Morbid obesity	750	0	0	0	0	11/15	5/13
5	WHC# A91-91	41	B	M	+*	0	+	Atherosclerotic CAD	450	3	0	0	+(5)	11/13	3/11
6	WHC# A89-89	57	B	M	0	+	0	Chronic CHF	590	1	0	+	0	6/9	6/11
7	DCVAH# 87A-54	62	B	M	0	+	+	Chronic renal failure	525	0	0	+	+(3)	7/12	6/11
8	SH# A90-15	79	W	F	0	+	0	Chronic CHF	525	1	0	0	+(3)	8/11	5/10

*Died in cardiac catheterization laboratory shortly after angioplasty.
A = chronic alcoholism; CAD = coronary artery disease; CAs = coronary arteries; CHF = congestive heart failure; CSA = cross-sectional area; F = fibrosis; HW = heart weight; LADCA = left anterior descending coronary artery; LCCA = left circumflex coronary artery; LV = left ventricular; N = necrosis; RCA = right coronary artery; SD = sudden death; SH = systemic hypertension; WPW = Wolff-Parkinson-White.

plasia of both right and left circumflex coronary arteries. Certain findings in these 8 patients will be described here.

Pertinent findings in the 8 patients are summarized in Table I. The patients ranged in age from 26 to 79 years (mean 46). Seven were black men and 1, a white woman. At least 5 by history had had systemic hypertension. One (patient 1, Table I) had a severely stenotic unicuspid aortic valve. Patient 3 had an episode of supraventricular tachycardia 4 months before death, and electrocardiograms, after slowing of the heart rate, were typical of the Wolff-Parkinson-White syndrome. Patient 4 weighed 386 pounds (175 kg). Three patients had narrowing of 1 or more major epicardial coronary arteries >75% in cross-sectional area by atherosclerotic plaque: in patient 5 the right, left anterior descending, and left circumflex coronary arteries were severely narrowed; in patient 6, significant (>75%) luminal narrowing was limited to the distal portion of the left circumflex coronary artery and in patient 8, the left anterior descending was narrowed just over 75% in cross-sectional area by plaque. Two of the 3 patients underwent coronary balloon angioplasty. Grossly visible left ventricular scars were present in 2 patients: in patient 6 the healed myocardial infarct was large, transmural and posterior; in patient 7 the healed infarct was small, nontransmural (mainly subepicardial) and posterior. Thorough examination of the major epicardial coronary arteries in patient 7 disclosed insignificant (<50% cross-sectional area reduction) luminal narrowing. Five of the 8 patients died suddenly: 3 (patients 2, 3 and 4) were found dead at home, and when each was last seen alive they appeared in their usual state of health; 1 (patient 1), who had severe aortic valve stenosis, had fatal cardiac arrest while dancing in a disco; and 1 (patient 5) had fatal cardiac arrest in a cardiac catheterization laboratory shortly following insertion of a stent (after unsuccessful balloon angioplasty) for severe coronary arterial narrowing from atherosclerosis.

At necropsy, the heart weight was increased (>400 g) in all 8 patients (mean 573 g) (Table I). The left anterior descending coronary artery in all 8 patients appeared of a size expected for the weight of the heart. In 6 of the 8 patients the left anterior descending coronary artery coursed past the left ventricular apex to ascend on the

posterior surface of the heart for distances ranging from 2 to 5 cm (Table I). The right and left circumflex coronary arteries, of course, were small and neither coursed to the crux posteriorly. The right coronary artery remained in the right atrioventricular sulcus for distances varying from 6 to 11 cm (mean 8) (Table I). These distances, compared with the total potential lengths of the right coronary artery from its ostium in the aorta to the crux posteriorly, indicate that this artery remained in the atrioventricular sulcus for 50 to 85% (mean 68%) of the potential distance within the atrioventricular sulcus from its aortic origin to the crux posteriorly. The left circumflex coronary artery remained in the left atrioventricular sulcus for distances varying from 3 to 9 cm (mean 6) (Table I), numbers indicating that the left circumflex coronary artery was located within the left atrioventricular sulcus for 27 to 75% (mean 54%) of the total potential length of the left atrioventricular sulcus from the origin of the left circumflex from the left main coronary artery to the crux posteriorly.

Hypoplasia of both right and left circumflex coronary arteries, to our knowledge, has never been reported angiographically. It was first reported at necropsy by Maron and associates[1] in a 17-year-old girl who died suddenly just after completing a 3-mile race. The only cardiac abnormality observed at necropsy was bilateral hypoplasia of the 2 major coronary arteries. Menke and colleagues[2] reported a 30-year-old man who died suddenly during a basketball game, and necropsy disclosed hypoplasia of both right and left circumflex coronary arteries. Each of these 2 arteries was described as being "half their normal length." No other potential functionally significant cardiac abnormalities were found at autopsy in the patient reported by Menke et al.

In the 8 patients reported herein only 3 (patients 5, 6 and 8) had had a coronary angiogram during life, and bilateral hypoplasia of the right and left circumflex coronary was not suspected from this study in any of them. Of the 8 necropsy patients, it appears likely that the bilateral coronary hypoplasia was of functional significance in 2 patients (nos. 2 and 7 [Table I]). Although 5 of the 8 patients died suddenly, a cause other than bilateral coronary hypoplasia was present in 4 of them. Patient 2, however, died suddenly and a cardiac condition other

than bilateral coronary hypoplasia was absent. Two of the 8 patients had grossly visible left ventricular scars (healed myocardial infarcts): one of them (patient 6), however, had severe coronary atherosclerosis, but the other (patient 7) had no explanation for the left ventricular scar other than bilateral coronary hypoplasia.

Hypoplasia of a major epicardial coronary artery appears, with one exception, to be limited to the right and left circumflex coronary arteries. We have not observed or seen reported hypoplasia of the left anterior descending artery as long as it arose normally from the left main coronary artery, which in turn arose normally from the aorta. If, however, a single coronary artery arises from the aorta and if that single artery begins as a normally originating and coursing right coronary artery that continues past the crux as the left circumflex coronary artery, which when reaching the anterior surface of the heart continues as the left anterior descending coronary artery, the latter artery may become hypoplastic because this artery courses distally and approaches the cardiac apex (Figure 2).[3]

In the present study we defined hypoplasia to include 2 factors: (1) *small sized arteries*, and (2) *shorter courses*

so that *neither reached the crux* (at the midportion of the atrioventricular groove posteriorly). We have observed at necropsy, however, at least 2 other patients with severe hypoplasia of both right and left circumflex coronary arteries, but 1 of the 2 arteries, despite their small sizes, nevertheless reached the cardiac crux. Although it could be argued that these type cases also constitute bilateral coronary hypoplasia, we believe it better to apply our more limited definition to this uncommon occurrence.

In summary, the hearts from 8 patients are described with hypoplasia of both right and left circumflex coronary arteries. It appeared that 2 of the 8 had evidence of myocardial ischemia as a direct consequence of the bilateral hypoplasia.

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Frequency of Thromboembolic Stroke in Persons ≥60 Years of Age with Extracranial Carotid Arterial Disease and/or Mitral Annular Calcium

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Patients with extracranial internal or common carotid arterial disease have an increased incidence of ischemic stroke.[1-4] Patients with mitral annular calcium (MAC) have an increased incidence of thromboembolic stroke.[5-7] We are reporting the results from our prospective study associating extracranial internal or common carotid arterial disease and MAC with the incidence of new thromboembolic stroke at 45-month follow-up.

Technically adequate bilateral carotid duplex ultrasonograms and M-mode and 2-dimensional echocardiograms for detecting MAC were obtained prospectively in 928 unselected elderly patients (663 women and 265 men), mean age 82 ± 8 years (range 60 to 101), in a long-term health care facility. Bilateral carotid duplex ultrasonograms were performed as previously described with an Interspec XL machine, using a 7.5 MHz transducer having combined 2-dimensional real-time and pulsed- or high-pulse frequency Doppler capabilities.[8] The severity of extracranial carotid disease was semiquantified by using conventional Doppler criteria (Vmax <0.80 m/s = <40% arterial luminal diameter reduction; Vmax 0.80 to 1.75 m/s = 40 to 80% arterial luminal diameter reduction; Vmax >1.75 m/s = 80 to 99% arterial luminal diameter reduction; Vmax 0.00 m/s [no Doppler signal on ≥2 separate tests] = 100% arterial luminal diameter reduction). MAC was diagnosed as previously described.[6]

New thromboembolic stroke was diagnosed by a neurologist if a focal neurologic event occurred suddenly but without prolonged unconsciousness, nuchal rigidity, fever, pronounced leukocytosis or bloody spinal fluid.[9] The focal neurologic signs of ischemic stroke were explained by loss of function in a restricted area of the brain corresponding to a particular vascular territory. Thromboembolic stroke was also confirmed by computerized axial tomography in 193 of 203 patients (95%). Thromboembolic stroke was diagnosed by clinical criteria only in the remaining 10 patients (5%). Cerebral transient ischemic attack was diagnosed by a neurologist if the patient developed transient (<24 hours), contralateral (to the extracranial carotid disease) hemiparesis or hemianesthesia, or transient ipsilateral blindness or visual field defect.

None of the patients with extracranial carotid disease in this study underwent carotid endarterectomy. Aspirin 325 mg/day was prescribed to 145 of 150 patients (97%) with extracranial carotid disease. Mean follow-up was 45 ± 21 months (range 3 to 64). Chi-square analysis was used to analyze data.

Forty to 100% extracranial carotid disease was present in 47 of 265 men (18%), in 103 of 663 women (16%) (p = not significant), and in 150 of 928 patients (16%). MAC was present in 361 of 663 women (54%), in 105 of 265 men (40%) (p <0.001), and in 466 of 928 patients (50%). Prior stroke occurred in 72 of 150 patients (48%) with 40 to 100% extracranial carotid disease, and in 212 of 778 patients (27%) with 0 to 40% extracranial carotid

TABLE I Prevalence of Mitral Annular Calcium in Elderly Patients With and Without Extracranial Internal or Common Carotid Arterial Disease		
	Mitral Annular Calcium	
Extracranial Carotid Arterial Disease	No.	(%)
40 to 100% (n = 150)	101	(67)*
0 to 40% (n = 778)	365	(47)

*p <0.001 comparing the prevalence of mitral annular calcium in patients with 40 to 100% and 0 to 40% extracranial carotid disease.

TABLE II Incidence of New Thromboembolic Stroke and of Cerebral Transient Ischemic Attack at 45-Month Follow-Up in Elderly Patients With and Without Extracranial Internal or Common Carotid Arterial Disease and With and Without Mitral Annular Calcium (MAC)					
Extracranial Carotid Arterial Disease	MAC	New Thromboembolic Stroke		New Cerebral Transient Ischemic Attack	
		No.	(%)	No.	(%)
40 to 100%	+	52/101	(51)	8/101	(8)
40 to 100%	0	16/49	(33)	3/49	(6)
0 to 40%	+	88/365	(24)	11/365	(3)
0 to 40%	0	47/413	(11)	3/413	(1)

For thromboembolic stroke: p <0.05 comparing patients with 40 to 100% carotid disease with and without MAC; p <0.001 comparing patients with 40 to 100% and 0 to 40% carotid disease with and without MAC; p <0.001 comparing patients with 40 to 100% and 0 to 40% carotid disease and no MAC; p <0.001 comparing patients with 0 to 40% carotid disease with and without MAC.
For cerebral transient ischemic attack: p <0.05 comparing patients with 40 to 100% disease and 0 to 40% carotid disease with MAC; p <0.001 comparing patients with 40 to 100% control disease with MAC, and 0 to 40% control disease without MAC; p <0.005 comparing patients with 40 to 100% and 0 to 40% carotid disease with no MAC; p <0.02 comparing patients with 0 to 40% carotid disease and with and without MAC.

disease (p <0.001). New thromboembolic stroke oc-
curred in 61 of 265 men (23%), in 142 of 663 women
(21%) (p = not significant), and in 203 of 928 patients
(22%). New cerebral transient ischemic attack occurred
in 12 of 265 men (5%), in 13 of 663 women (2%) (p
<0.05), and in 25 of 928 patients (3%).

Table I shows the prevalence of MAC in patients with
and without extracranial carotid disease. Table II states
the incidence of new thromboembolic stroke and of new
cerebral transient ischemic attack in patients with extra-
cranial carotid disease with and without MAC, and in
patients with no extracranial carotid disease with and
without MAC.

MAC has been linked to cerebral ischemic events but
considered by some investigators to be more likely a
marker of other vascular disease causing stroke than the
primary embolic source.[10] However, to the best of our
knowledge, an association between extracranial carotid
disease and MAC has not been previously reported. In
our study, the prevalence of MAC was increased 1.4
times in elderly patients with extracranial carotid disease
than in elderly patients without extracranial carotid dis-
ease.

Patients with extracranial carotid disease or an
asymptomatic carotid bruit have an increased incidence
of ischemic stroke.[1-4] In our study, the incidence of new
thromboembolic stroke was 2.6 times higher in elderly
patients with 40 to 100% extracranial carotid disease
than in elderly patients without extracranial carotid dis-
ease.

In 3 prospective studies, the incidence of new cerebro-
vascular events was increased 5.0 times,[5] 1.7 times,[6] and
4.0 times[7] in patients with than without MAC. In our
study, the incidence of new thromboembolic stroke was
2.2 times higher in patients with than without MAC, 1.5
times higher in patients with 40 to 100% extracranial
carotid disease with than without MAC, and 2.2 times

higher in patients with than without MAC and no extra-
cranial carotid disease. Finally, the incidence of new
thromboembolic stroke was 4.6 times higher in elderly
patients with 40 to 100% extracranial carotid disease and
MAC than in elderly patients with no extracranial carot-
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Echocardiographic Frequency and Severity of Aortic Regurgitation After Ultrasonic Aortic Valve Debridement for Aortic Stenosis in Persons Aged >65 Years

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Mechanical debridement of stenotic aortic valves was performed before the availability of prosthetic valves, but was limited by recurrent stenosis.[1,2] However, aortic valve debridement remains useful for patients with small aortic annulae unsuitable for a prosthetic valve or with contraindications to anticoagulation. Recently, the use of ultrasonic energy to decalcify the aortic valve successfully relieved obstruction, but aortic regurgitation (AR) developed during short-term follow-up.[3-7] This study evaluates the long-term results of ultrasonic aortic valve decalcification for aortic stenosis.

Twenty consecutive patients (11 women and 9 men, mean age 77 ± 5 years, range 67 to 85) undergoing ultrasonic aortic valve decalcification between 1988 and 1990 were evaluated. Mean preoperative aortic valve area was 0.8 ± 0.3 cm², with a mean gradient of 43 ± 22 mm Hg at cardiac catheterization. No patient had more than trivial AR. Most patients (14 of 20) were limited by New York Heart Association class III to IV symptoms of dyspnea. Mean ejection fraction was 56 ± 16%. Selection for debridement was based on small aortic annular size, contraindications to anticoagulation, or at least moderate aortic stenosis when performed as an adjunct to coronary artery bypass grafting. Standard hypothermic extracorporeal circulation and cold cardioplegic arrest were followed by oblique aortotomy. The Cavitron Ultrasonic Surgical Aspirator (Cavitron Surgical Systems, Inc., Stamford, Connecticut) was used to deliver ultrasonic energy and disintegrate valvular calcium. Continuous irrigation suspended the particulate matter and cooled the site of debridement. Complete debridement was performed to restore normal leaflet mobility.

Echocardiograms obtained before discharge and at the most recent follow-up visit were analyzed in a blinded manner by 2 cardiologists. Maximal aortic velocity was obtained through continuous-wave Doppler sampling. The systolic left ventricular outflow tract diameter was measured in the parasternal long-axis view at the aortic hinge point, with velocity assessed in the apical 5-chamber view by pulsed Doppler sampling just below the aortic valve. Aortic valve areas were then calculated using the continuity equation.[8] AR severity was determined using 3 Doppler methods: color flow analysis of the ratio of AR jet to left ventricular outflow tract height (≤0.25 = trivial; 0.25 to 0.46 = mild; 0.47 to 0.64 =

moderate; and ≥0.65 = severe)[9]; deceleration slope (cm/ s) (≤2 = mild; >2 but <3.5 = moderate; and ≥3.5 = severe)[10]; and analysis of reversal of flow in the aortic lumen in the suprasternal view (absence of diastolic flow reversal = mild; presence in initial 50% of diastole = moderate; and holodiastolic = severe).[11] AR was then quantified as follows: 1 = trivial; 2 = mild; 3 = moderate; and 4 = severe. All charts were reviewed, and physicians and their respective patients were contacted to obtain follow-up data including age, sex, New York Heart Association functional class, occurrence of cerebrovascular accident, endocarditis, reoperation or death.

Clinical and echocardiographic data for each patient are summarized in Table I. Data in the text are expressed as mean ± SD. The paired Student's t test was used for analysis of variables, with a p level <0.05 considered significant. Ultrasonic aortic valve decalcification was accompanied by coronary artery bypass grafting in 16 of 20 patients (80%) and by mitral valve repair in 3 (15%). Perforation of aortic valve cusps needed pericardial patch repair in 9 patients (45%). Of 3 patients (15%) who died before hospital discharge, 1 had a myocardial infarction after 2 days, and another had an embolic stroke immediately after surgery, with mild AR, myocardial infarction and ventricular fibrillation at 53 days (both confirmed at autopsy). The third patient died after 55 days, with congestive heart failure and ventricular fibrillation. Seventeen patients survived and were discharged from the hospital.

Echocardiograms were obtained in 18 patients within 2 weeks after surgery; however, analysis was limited to technically adequate studies. AR could be assessed in 17 patients. In 4 of 17 patients (24%), grade 2 AR was present, with none having ≥ grade 3 AR. Aortic mean gradients were measured in 14 patients and decreased to a mean of 17 ± 9 mm Hg from a mean preoperative gradient of 43 ± 22 (p = 0.0001). Estimates of aortic valve area were obtained in only 8 patients owing to technical limitations, yielding a mean preoperative area of 0.8 ± 0.3 cm², which increased to 1.1 ± 0.5 after surgery (p = 0.2).

The clinical status of all patients was assessed, with a mean follow-up of 12 months (range 2 days to 33 months). In addition to the 3 in-hospital deaths, 6 late deaths occurred, resulting in a total mortality of 9 of 20 (45%). Of the 6 late deaths, all had congestive heart failure, and 5 had mild to moderate AR. The presence of AR was undetermined in the sixth patient. One patient died after reoperation for AR, constrictive pericarditis and congestive heart failure (Table I, patient 3). In all, 3 patients (15%) needed reoperation for AR and conges-

TABLE I Clinical and Echocardiographic Results of Aortic Valve Debridement

Pt. No.	Age (yr) & Sex	Aortic Mean Gradient (mm Hg)			Severity of AR			Other Procedures	Clinical Outcome
		Pre	Post	F/U	Pre	Post	F/U		
1	85 F	67	13	16	1	1	4	CABG	R
2	82 F	39	30	—	0	0	—	CABG	D
3	79 M	21	15	13	0	0	2	CABG	R, D
4	78 F	49	—	33	0	0	3	—	D
5	83 M	95	15	18	0	2	3	CABG	A
6	78 F	19	13	17	1	2	3	CABG, MVR	D
7	84 F	70	13	22	0	0	3	—	A
8	78 M	35	3	34	0	0	2	CABG	A
9	78 F	36	22	—	0	2	—	—	D
10	72 M	23	—	9	0	0	2	CABG	D
11	78 F	30	—	—	0	—	—	—	D
12	72 M	42	9	20	0	2	4	CABG, MVR	R
13	78 F	80	—	—	0	1	—	CABG	D
14	80 M	25	16	26	0	1	2	CABG	A
15	67 F	15	—	34	0	—	3	CABG	A
16	83 F	55	42	26	0	1	2	CABG	A
17	72 F	53	—	26	1	—	2	CABG	A
18	69 M	23	18	15	0	0	1	CABG	A
19	80 M	51	13	18	0	1	4	CABG, MVR	A
20	72 M	32	15	—	0	0	2	CABG	D

A = alive; AR = aortic regurgitation; CABG = coronary artery bypass graft surgery; D = dead; F/U = late follow-up; MVR = mitral valve repair; R = reoperation.

TABLE II Comparison of Clinical Outcomes After Ultrasonic Aortic Valve Debridement

Investigators	No. of Pts.	Mean F/U (mos.)	≥ Moderate AR (%)	Reoperation (%)	Mortality (%)
Schwinger et al[3]	10	3	60	40	0
Scott et al[4]	8	6	0	13	0
McBride et al[5]	22	6	87	9	23
Craver[6]	11	—	—	27	36
Freeman et al[7]	61	9	63	14	22
Present study	20	12	56	15	45

AR = aortic regurgitation; F/U = follow-up.

tive heart failure. Late embolic events needed anticoagulation in 2 patients. No patient developed endocarditis. Of the 9 patients who survived and did not undergo reoperation, all are in New York Heart Association class I or II. Significantly, all 9 patients have AR, and 4 (45%) have ≥ grade 3 severity.

After the 3 early postoperative deaths, 17 patients remained in the follow-up group. Echocardiograms were obtained in 16 patients at a mean follow-up of 14 months (range 3 to 26) from the time of surgery. All 16 patients had AR, and 9 (56%) had grade 3 to 4 severity. This represents a significant increase in AR compared with before surgery (p = 0.0001). The mean aortic gradient was successfully obtained in 15 patients and averaged 22 ± 8 mm Hg, which was significantly reduced from before surgery (43 ± 22; p = 0.005). Due to technical limitations, aortic valve areas were calculated in only 7 patients. The mean preoperative aortic valve area of 0.8 ± 0.3 cm² in these patients was minimally increased to 0.9 ± 0.4 at follow-up. Because aortic valve areas were obtainable in <50% of the follow-up group, the absence of change in valve area may not be representative of the entire group.

These findings are consistent with previous reports (Table II). Schwinger et al[3] evaluated 10 patients at 26 days and found severe AR in 2 cases. At 99 days, 4 more patients developed severe AR. In all, 4 patients in that series needed subsequent aortic valve replacement. At 6 months, Scott et al[4] found only a mild increase in the grade of AR, but McBride et al[5] found the incidence of mild and moderate AR to increase from 50 to 87% of patients. Furthermore, Craver[6] noted that 3 of 11 patients (27%) needed aortic valve replacement owing to AR; total mortality was 36%. Freeman et al[7] found severe AR in 26% of patients and moderate AR in 37% after 9 months of follow-up. Aortic valve replacement owing to severe AR was performed in 14% of these patients. The total mortality in that series was 22%.

Our study verifies the problem of progression of AR and its associated adverse clinical outcome after ultrasonic valve debridement. Comorbid disease in this elderly population contributed to the high mortality rate of 45%. In addition to the 3 early deaths, there were 6 late deaths, all with congestive heart failure, and 5 with significant AR. All patients who underwent follow-up echocardiography had AR, with 56% having moderate to severe AR. A subset of 9 patients have done well and remain in New York Heart Association class I or II, but all have AR (45% moderate to severe AR). Because of the frequent occurrence of progressively severe AR, and the high reoperation and mortality rates, we have abandoned this procedure and recommend that other clinicians do so also.

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Sinus Node Artery Occlusion for Treatment of Chronic Nonparoxysmal Sinus Tachycardia

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Chronic nonparoxysmal sinus tachycardia has been described as an inappropriate and persistent sinus tachycardia that is not related to organic, physiologic and adrenergic states or automatic dysfunction. Some cases are very symptomatic and refractory to conventional therapy. In this report, we describe an unusual therapy for a refractory case of chronic nonparoxysmal sinus tachycardia.

A 43-year-old woman was referred because of disabling palpitations for 18 years. She had had 20 hospital admissions related to sinus tachycardia. Drug therapy included digoxin, propranolol (480 mg), nadolol (80 mg), metoprolol (200 mg), verapamil (240 mg) and amiodarone (600 mg), alone and in combination. Physical examination and laboratory evaluation were normal. Electrocardiograms and Holter monitoring always showed sinus tachycardia, and during Holter monitoring, heart rate variation was trivial (≤ 10 beats/min). Exercise testing was normal. An electrophysiologic study demonstrated normal atrial activation sequence and no preexcitation. No arrhythmia was induced by atrial and ventricular programmed stimulation. Echocardiographic and coronary angiography were normal.

Transcoronary ablation of the sinus node was performed by selective catheterization of the sinus node artery, using a 20 mm LPS balloon (USCI) (Figure 1) introduced through a steerable guidewire (0.014 inch), using standard percutaneous transluminal coronary angioplasty techniques. This procedure produced junctional rhythm followed by atrial fibrillation, chest pain and elevation of the ST segments in the inferior leads. We removed the angioplasty system, and coronary angiography showed that the right coronary artery was patent (Figure 1C). The patient remained in the catheterization laboratory for 3 hours. During this period, angiography revealed proximal occlusion of the sinus node artery, and normal right and left coronary arteries, left ventriculography, and intraatrial and intraventricular pressures.

Chest pain and ST-segment elevation resolved after 4 hours. Bedside and Holter monitoring showed atrial fibrillation for 10 hours, after which sinus rhythm resumed. Laboratory evaluation showed electrocardiographic (inferior leads) and enzymatic changes compatible with myocardial infarction. Sinus tachycardia was easily controlled with propranolol (80 mg/day).

An echocardiogram was normal. A technetium-99m pyrophosphate scan disclosed abnormal uptake in the inferior wall. A coronary arteriogram performed 21 days after the initial procedure revealed a normal left ventriculogram and a patent sinus node artery.

The patient was asymptomatic for 4 months after the procedure. Her symptoms then recurred, and Holter monitoring showed sinus tachycardia (rates persistently >120 beats/min) for >50% of the recording. The dose of propranolol was increased, but the symptoms persisted.

Cardiac catheterization was repeated 9 months after the initial pro-
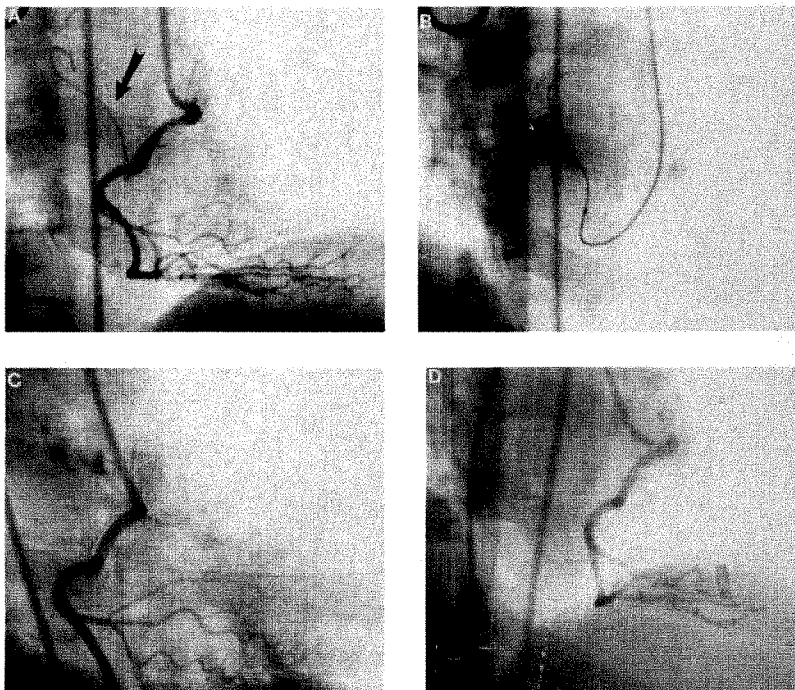
FIGURE 1. Mechanical ablation of sinus node artery. A, right coronary artery is shown, and sinus node artery is indicated (arrow). B, angioplasty catheter is shown placed in sinus node artery. C, sinus node artery is totally occluded. Picture was obtained immediately after removal of angioplasty system. D, right coronary angiogram is shown 3 hours after initial procedure. Proximal occlusion of sinus node artery is still seen, but right coronary artery is normal.

cedure and was normal (Figure 2). Transcoronary ablation of the sinus node was performed by selective catheterization of the sinus node artery, using a 20 mm mini-profile balloon (USCI) and our previous technique (Figure 2B). A 96% sterile ethanol solution was infused directly in the sinus node artery. This immediately produced junctional rhythm (70 beats/min) and moderate chest pain for 1 hour. Angiography showed distal occlusion of the sinus node artery (Figure 2D).

Immediate follow-up showed a normal echocardiogram, very brief and modest enzyme elevation, and a normal technetium-99m pyrophosphate uptake. Continuous Holter monitoring for 72 hours showed junctional rhythm with a mean heart rate of 66 beats/min and several episodes of accelerated idioventricular rhythm (noted during first 24 hours only) after the ablation (Figure 3).

Coronary angiography 18 days after chemical ablation showed total occlusion of the sinus node artery (Figure 4).

The patient remained asymptomatic in junctional rhythm at a heart rate of 70 beats/min for 12 months after the second ablation procedure. Subsequently, she noted episodes of dizziness, and a syncopal episode occurred. Subsequent monitoring during other syncopal episodes showed junctional rhythm (55 beats/min). An AAI-R pacemaker was implanted, and she has subsequently been asymptomatic without medications for 6 months after pacemaker implantation.

Chronic nonparoxysmal sinus tachycardia can occur in the absence of identifiable organic disease and may reflect relatively localized automatic dysfunction.[1] Some patients may be extremely symptomatic and resistant to all drug therapy. Disability resulting from refractory chronic sinus tachycardia can be a difficult clinical problem, and aggressive medical and surgical management have been reported for this particular problem.[2]

Conventional percutaneous coronary angioplasty techniques have been used to produce ischemia or interruption of blood supply to arrhythmogenic areas of the heart.[3-5] A pre-
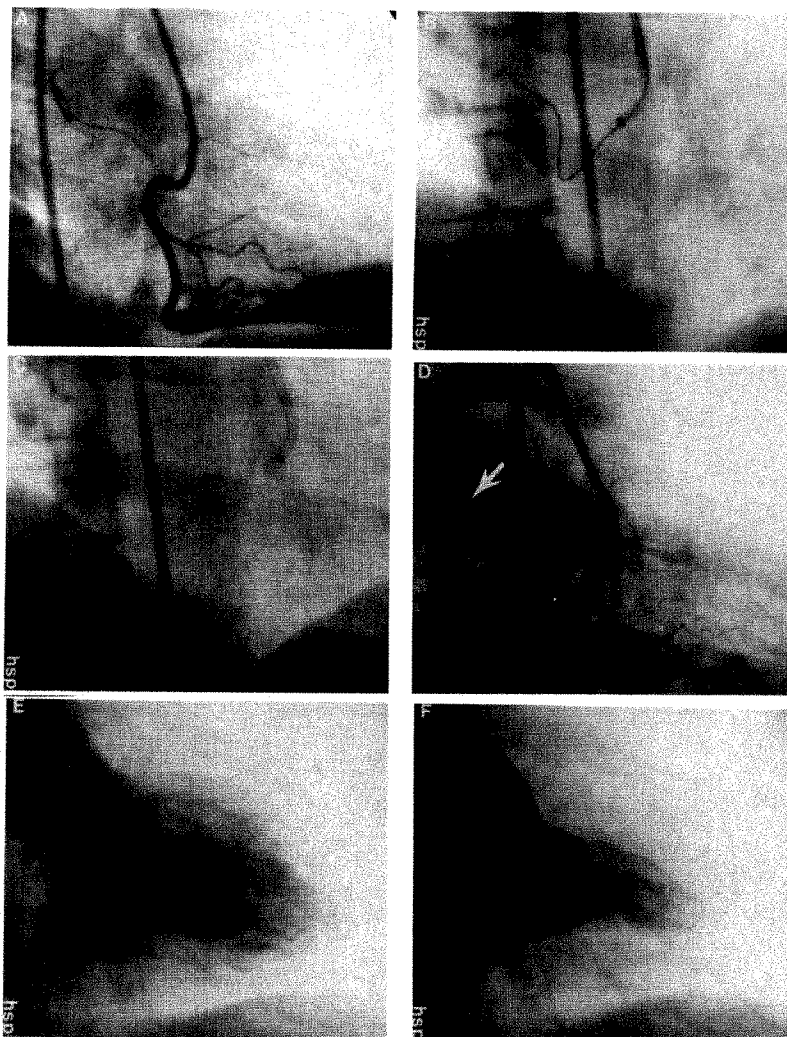
FIGURE 2. Chemical ablation of sinus node artery. A, right coronary artery with normal sinus node artery can be seen. Angiogram was obtained before any procedure was performed. B, angioplasty catheter is seen placed in sinus node artery. Sterile ethanol has been infused in coronary sinus artery. D, arrow indicates level of occlusion of coronary sinus artery. Ethanol injection resulted in distal occlusion of sinus node artery. E and F, diastolic and systolic frames in right anterior oblique left ventriculogram. Contraction pattern is normal.
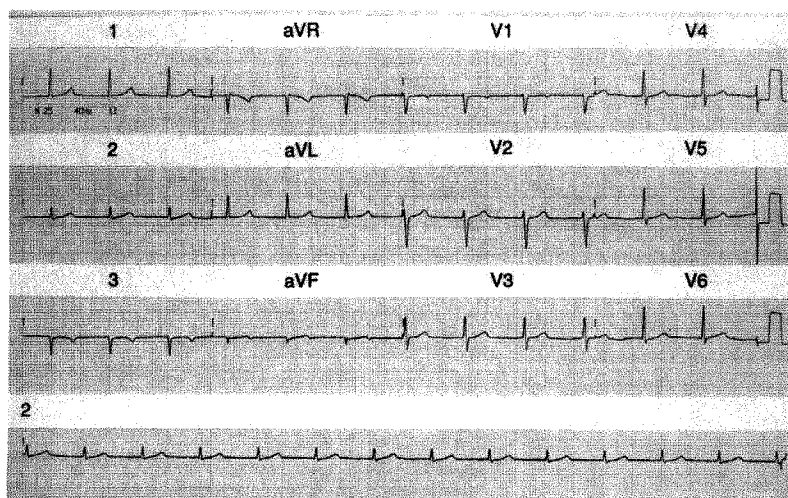
FIGURE 3. Twelve-lead electrocardiogram showing junctional rhythm obtained after chemical ablation of sinus node artery. Junctional rhythm at rate of 75 beats/min is shown.
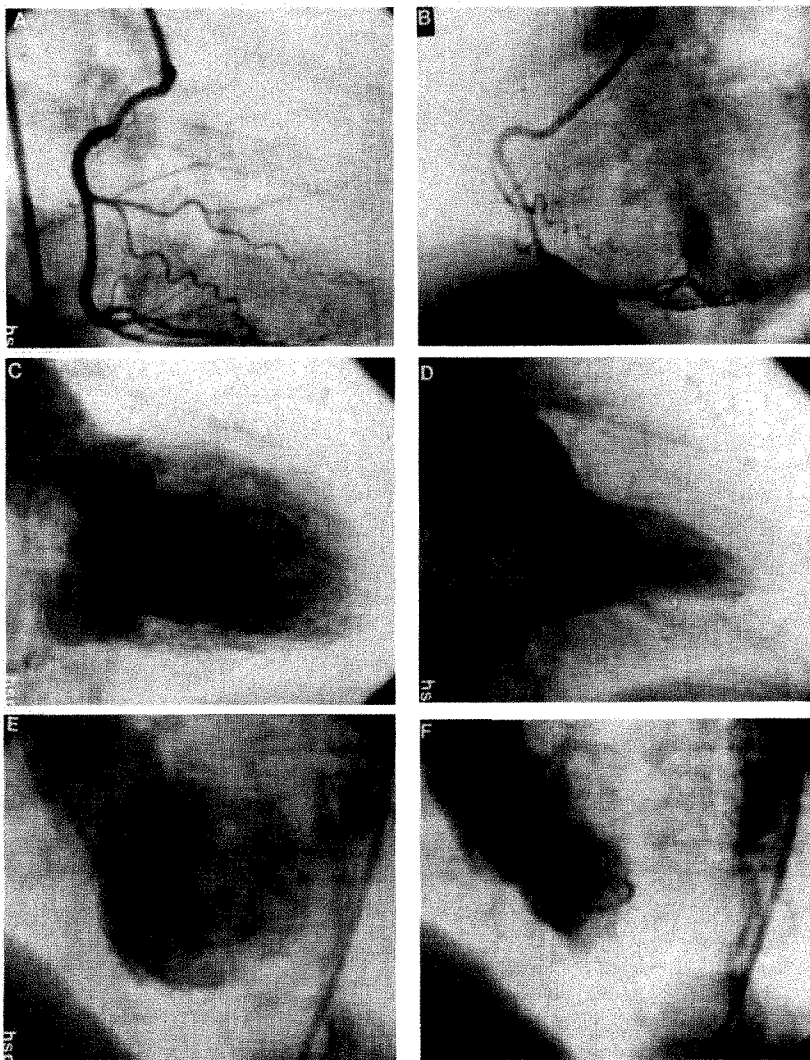
FIGURE 4. Follow-up angiogram performed 18 days after chemical ablation. *A* and *B*, no evidence of sinus node artery, and it is totally occluded at its origin. *C* and *D*, diastolic and systolic frames in right anterior oblique projection of left ventriculogram. *E* and *F*, diastolic and systolic frames from left anterior oblique left ventriculogram. Both are normal.

liminary experience with transcoronary chemical ablation of ventricular tachycardia using ethanol infusion in the tachycardia-related vessel has also been reported.[5] The risks of transmural myocardial necrosis produced by ethanol in the ventricle are probably different from those in the atrium where the muscle is thin, and complications such as rupture may be an important limitation for ethanol infusion.

In this case, mechanical occlusion of the proximal sinus node artery produced clinical, electrocardiographic and enzymatic evidence of infarction. There was only partial success in the control of the arrhythmia. Subsequent chemical ablation with ethanol produced no worse initial sequelae, and much better and sustained clinical arrhythmia control.

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Intraventricular Muscle Band Mimicking Asymmetric Ventricular Septal Hypertrophy and Hypertrophic Cardiomyopathy

Barry J. Maron, MD, Heinrich G. Klues, MD, and Charles McIntosh, MD, PhD

Asymmetric thickening of the anterior ventricular septum is the most characteristic morphologic feature of hypertrophic cardiomyopathy (HC).[1–3] The diagnosis of HC is frequently made clinically by the echocardiographic identification of this

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feature.[1] However, a number of pitfalls have been recognized as interfering in the precise quantification of septal thickness by echocardiography.[4,5] The present report illustrates one such example of unusual left ventricular anatomy creating the mistaken impression that HC may have been present in a patient with bacterial endocarditis.

A 37-year-old horse trainer (shortly after an elective inguinal hernia repair) incurred the sudden onset of fever and chills associated with signs and symptoms of congestive heart failure. These included exertional dyspnea and chest pain, orthopnea, pedal edema and paroxysmal nocturnal dyspnea, as well as night sweats, fever and substantial weight loss. There were also 2 episodes consistent with peripheral septic embolization. On physical examination, murmurs typical of aortic and mitral regurgitation and an S_2 gallop were heard.

Echocardiographic examination demonstrated apparent vegetations on both aortic and mitral valves, as well as systolic anterior motion of the anterior mitral leaflet (Figure

FIGURE 1. Two-dimensional echocardiograms obtained in the parasternal long-axis view. *A*, echo-dense anterior mitral leaflet with vegetation, showing systolic anterior motion and mitral-septal contact. Ventricular septum (VS) appears thickened. *B*, at end-diastole, in a slightly rotated cross-sectional plane that allows discrimination of the muscular band *(arrows)* from the true ventricular septum that appears to be of normal thickness. Calibration marks are 1 cm apart. LA = left atrium; LV = left ventricle.

FIGURE 2. M-mode echocardiograms showing morphologic appearance of anterior ventricular septum (VS) in the patient described. *A* and *B*, VS appears thickened (to 20 mm) due to contributions from true VS and the muscular band (MB), which appear to be contiguous in this plane; *C* and *D*, after mild angulation of the transducer the muscular band *(arrows)* has been separated from the true VS, which now appears to be of normal thickness (10 mm). Calibration marks are 1 cm apart. LV = left ventricle; MV = mitral valve; PW = posterior left ventricular free wall.

1). On this initial evaluation the anterior ventricular septum was judged to be increased in thickness (to 20 mm); left ventricular free wall thickness was normal (<12 mm). These observations, in association with the mitral systolic anterior motion and the awareness that bacterial endocarditis may occur in HC,[6] raised the diagnostic possibility of associated HC. However, a subsequent echocardiographic study defined (by fine rotation of the transducer) a distinct hypertrophied anomalous muscle band situated in close parallel relation to the anterior ventricular septum, which could be visualized in both parasternal long- and short-axis views (Figures 1 and 2). This large muscle bundle appeared to in-

sert in the most cephalad aspect of the anterior ventricular septum at the junction of septum with the anterior wall of the aortic root, and to extend distally to the region of the left ventricular apex. Thus, the "true" ventricular septal thickness was 10 mm and that of the anomalous muscle bundle was also 10 mm.

Six blood cultures all proved to be negative. Consequently, the decision was made to perform both mitral and aortic valve replacement with St. Jude prostheses. The valve specimens showed calcified vegetations in all 3 aortic leaflets and a large calcified vegetation on the anterior mitral leaflet.

This case illustrates an instance in which a large intraventricular muscle band was responsible for diagnostic uncertainty regarding the assessment of true ventricular septal thickness by echocardiography, and for a period of time contributed to the erroneous diagnosis of HC. Such a case emphasizes the importance of being aware

of such variability in ventricular morphology, as well as the need for careful echocardiographic interrogation of the septum with these issues in mind.

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Reversible Dilated Cardiomyopathy Due to Thyrotoxicosis

E. Joseph Bauerlein, MD, C. Simon Chakko, MD, and Kenneth M. Kessler, MD

Whether hyperthyroidism can cause a dilated cardiomyopathy remains controversial. It has been generally accepted that thyrotoxicosis may be associated with high output heart failure and may precipitate ischemia or heart failure in patients with either symptomatic or asymptomatic underlying heart disease. However, evidence for the development of a dilated cardiomyopathy in otherwise normal hearts is confined to animal models and the pediatric population.[1] Studies showing a decreased cardiac reserve on exercise by nuclear cardiographic studies are often quoted as evidence of occult myocardial dysfunction in hyperthyroid patients. The number of patients in these studies was small and predominantly female (15 of 19).[2,3] The fact that women do not consistently increase their ejection fraction with exercise[4] challenges the current interpretation of these results. We present a patient in whom thyrotoxicosis was accompanied by a reversible dilated cardiomyopathy.

A 57-year-old man with a history of borderline systemic hypertension was admitted to the hospital with increasing exertional dyspnea for 4 months. He had noted a 30-pound weight loss over 8 months. He weighed 100 pounds and was 69 inches tall. His legs and arms were warm and he had a mild tremor. Blood pressure was 130/78 mm Hg. The thyroid gland was firm and enlarged. The jugular veins were distended, and bibasilar rales, an S₃ gallop and leg edema were present. Chest x-ray showed cardiomegaly,

pulmonary venous hypertension and Kerley B lines. The electrocardiogram showed sinus tachycardia (heart rate = 126 beats/min), left anterior hemiblock, incomplete right bundle branch block and nonspecific ST-T-wave abnormalities. Thyroid function tests and a thyroid scan were consistent with hyperthyroidism secondary to Grave's disease. The initial echocardiogram showed left ventricular dilatation, a decreased shortening fraction and calculated left ventricular ejection fraction (Table I). Signs of heart failure responded promptly to furosemide, bed rest and sodium restriction. The thyrotoxicosis responded initially to super saturated potassium iodide and propylthiouracil but recurrent hyperthyroidism required repeated doses of radioactive I¹³¹ for control. Echocardiography 6 months later, at a time when the patient was euthyroid, showed normal left ventricular size and function, and a 34% increase in left ventricular mass. A thallium exercise test was totally normal.

Previous studies in hyperthyroid patients show the left ventricle to be typically hyperkinetic and hypertrophied.[1] The hypertrophy is apparently compensatory and reverses with treatment.[5] The current patient is a notable exception in that overt congestive heart failure was evident with the expected high cardiac output but with left ventricular dilatation and a moderately depressed left ventricular ejection fraction. The pathogenic mechanism responsible for this unusual response in this patient appears to be the presence of significant cardiac atrophy rather than the usual compensatory hypertrophy. With treatment, the patient's left ventricular mass increased and his left ventricular size and contraction normalized. We suggest that the hyperthyroidism was unusually severe as suggested by the marked elevation of the thyroxine level and resistance to treatment. Under these circumstances, there was significant weight loss accompanied by myocardial atrophy similar to that reported in anorexia nervosa.[6] This is the first report, to our knowledge, of a reversible congestive cardiomyopathy associated with hyperthyroidism in an adult without demonstrable underlying heart disease.

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TABLE I Clinical and Echocardiographic Findings

	Admission	6 Months
Weight (lb)	100	140
Height (in)	69	69
Heart rate (beats/min)	140	58
End-diastolic diameter (cm)	6.4	5.5
End-systolic diameter (cm)	5.4	3.5
Cardiac output (liters/min)	9.5	6.0
Shortening fraction	0.16	0.36
Ejection fraction (%)	32	74
Left ventricular mass (g)	163	218
T₄	46.7	7.4

Low-Dose Sustained Release Nicotinic Acid (Tri-B₃) and Lipoprotein (a)

There is a well-established relation between lipoprotein (a) (Lp[a]) levels and the risk of coronary artery disease.[1] Even though Lp(a) was discovered by Berg in 1963, it is only recently that some of its properties were characterized. Although many drugs are available to treat hyperlipidemia (resins, 3-hydroxyl-3-methyl glutaryl coenzyme A reductase inhibitors, fibrates), few drugs have been shown to significantly lower Lp(a) levels. In 1985 Gurukar et al[2] demonstrated that neomycin in combination with nicotinic acid significantly lowered Lp(a) levels. In 1989 Carlson et al[3] reported significant lowering of Lp(a) levels in subjects treated with 4 g of nicotinic acid. Whereas in large doses nicotinic acid lowers Lp(a) levels, it is often poorly tolerated. We wondered whether low-dose nicotinic acid would be useful in lowering Lp(a) levels.

In a randomized study, 20 subjects with mild hyperlipidemia (entry total cholesterol 6 to 8 mmol/liter) were treated with Tri-B₃ (Rhone Poulenc Rorer, Australia). Eleven subjects received 500 mg/day in divided doses for a period of 12 weeks. A second group of 9 subjects received (in divided doses) 500

mg/day for 3 weeks, then 1 g/day for 3 weeks, and finally 2 g/day for 6 weeks. We measured Lp(a) using antisera from Behring Australia and Immuno calibrators (Immuno AG, Austria) in a Behring nephelometer. The detection limit by this method is 120 mg/liter, and the coefficient of variation for the assay is 8%.

Although 500 mg of Tri-B₃ had no significant effect on total, low- and high-density cholesterols and apoproteins A₁ and B, it caused a significant decrease in Lp(a) levels (from 389 ± 84 to 288 ± 71 mg/liter). A summary of the 2 studies is shown in the accompanying table.

Our study demonstrates that even at a low dose (500 mg/day) of Tri-B₃ there is significant lowering of Lp(a) levels. At this dose, the drug is well tolerated, and only 1 patient complained of mild flushing.

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6 February 1992

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Results (% changes)

	500 mg (n = 11)	1 g (n = 9)	2 g (n = 7)
Total cholesterol	−2	−14*	−32*
Triglyceride	−6	−10	−20*
HDL cholesterol	+3	+6	+2
LDL cholesterol	−2	−21*	−43*
Apoprotein A₁	−1	+10†	+1
Apoprotein B	−3	−11*	−38*
Lp(a)	−24†	−33†	−67*

*p <0.001; †p <0.01.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a).

Less Money for Doctors in the Future?

Permit me to share some thoughts on Roberts' recent editorial summary of the first Ralph D. Alley lecture by Dr. Harry Schwartz.[1,2] Part of the difficulty the public has with physician incomes is in trying to reconcile the "good samaritan" heritage of the medical profession with unabashed entrepreneurship. But the problem of a bad image based on perceptions of greed and excessive remuneration may not entirely be restricted to non-physicians. It would be intructive, for example, to find out what cardiovascular surgeons think of interventional cardiologists and vice versa. On other fronts, there are subtle tensions between "cognitive" and "non-cognitive," and "academic" and "non-academic" physicians. Primary care careers seem to be unfashionable these days, even as concern is increasing for underserved populations in the country. These issues, among others, foster a lack of internal cohesion and make it easier for detractors to take shots at physicians as a whole. However, the discrepancy between negative public perceptions of physicians as a group, and the positive attitude of people to their own doctors, is strikingly reminiscent of the U.S. Congress. People seem to appreciate their own congressmen but do not necessarily think highly of the institution! Perhaps we can learn something from this.

That physicians in the foreseeable future will *not be allowed to do everything* to their patients that they are scientifically *able* to do is unfortunate. But if we are doing things we *can* do but *ought not* to be doing, society is in order to call our judgment into question. The current system encourages people to build their careers around specific items of technology, thus creating entire generations of "retail" physicians whose academic and practice profile is technologic and self-fulfilling. Many of us never seem to grasp the big picture. The impact of profit and technology-driven resource consumption on the inflationary ex-

cesses of the health care industry cannot be overemphasized. However, how do we ensure that in the panic of a society grouping for solutions to the health care crisis, we do not lose the professional flexibility of informed choice over the things we *should* be doing? In my opinion this is a more fundamental worry. After taking control of the tactical high ground, strategic issues of remuneration could be better addressed in the context of an overall settlement. To weather the gathering storm, we really ought to proceed from the premise that as members of the society, we are team players. If the society collapses, not only can we not prosper, but all our earnings would be meaningless, even if a savings plan is in place! We *should be seen* to be investing in the survival of the economy and the long-term health and comfort of the society at large. We should also be much more involved in shaping policy debates rather than being presented with administrative and fiscal *fait accompli*.

Although the U.S.A. is unique in the western world (excluding South Africa) in its inability to insure all its citizens and provide comprehensive access, it is arguably true that demand for health care is "unrestrained." This is partly because to a greater extent than other countries, every person regards it as a cradle-to-grave right to be the unit of decision making for whom physicians can bring the full range of resources to bear. There is also an assumption that high technology is synonymous with high quality. However, although not intuitively obvious, one of the interesting but less publicized characteristics of commodity-health economics is that supply may actually dictate or significantly influence demand.

The term "supply-mediated endless-loop economic tachycardia" may help characterize this phenomenon in the minds of cardiologists!

The health care complex has many components including patients, physicians and allied professionals, hospitals, the legal system, private and public insurers, as well as pharmaceutical and equipment manufacturers each of which has an effective lobby. Although we tend to assume that the patient is the only "consumer" of health care, this is not totally true. All components of the complex consume health care resources, and further their own agendas by influencing the physician-patient interface. Interaction and competition is multidirectional. The physician-patient relationship in our generation is, therefore, not an intimate one-on-one relationship. Although we like to think so, the physician is not always the revered source of information, comfort and salvation whose uncontested role is to pontificate about choices open to a patient. Because health care functions like a commodity, suppliers and consumers are beholden to numerous sources of pressure that shape their expectations and behavior. In seeking to reverse the downturn in our fortunes, some insight into the larger health care debate is in order. Estimates of administrative costs already vary from 10 to 25% of the still rising $700 billion yearly health care bill, while health care fraud may account for 10% of costs. The much heralded "well-insured" patient-consumer is bombarded by well over 1,000 health plans, and terms of coverage are getting slimmer by the day, particularly for nonhealthy patients. Risk selection rather than risk management has become the byword for health in-

surance. Meanwhile employers are grumbling about costs. On the other hand, the specter of litigation looms large in our medical decisions. In communicating with patients, therefore, where do we begin?

Regarding the British National Health Service (NHS) reform, Margaret Thatcher did not lose her job because "British Doctors communicated with British patients who made the Thatcher reform so unpopular that she lost her job. . . ." She lost her job due in part to the electoral fatigue that builds in when a politician stays too long in office, and also because her party rivals exploited a critical combination of events (notably the flat poll tax and her policy on Europe) to challenge her leadership and effect a parliamentary coup. The Conservative party sacrificed her rather than risk losing the general election at a time of public discontent in a recession economy!

The society has to decide whether health is a social right or just another item in the market. Issues like access, costs, tort and insurance reform, technology management, practice-guideline development and AIDS among others, will require coordination with the political leadership. As the debate for national health reform heats up, physicians need to be in the vanguard of sensitive and enlightened opinion. But we must first clean our own house.

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18 February 1992

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PREVENTIVE CARDIOLOGY

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Effectiveness of Low-Dose Colestipol Therapy in Patients with Moderate Hypercholesterolemia

H. Robert Superko, Philip Greenland, Ralph A. Manchester, Nicholas A. Andreadis, Gordon Schectman, Nancy Hendriksen West, Donald Hunninghake, William L. Haskell, and Jeffrey L. Probstfield

The effect of low-dose bile-acid binding resin treatment was investigated in women and men with moderate hypercholesterolemia (mean low-density lipoprotein [LDL] cholesterol 4.34 ± 0.28 mmol/liter). One hundred and fifty-two subjects were randomized to 1 of 4 treatment groups (placebo, and 5, 10 and 15 g/day of colestipol) for 12 weeks. LDL cholesterol reductions (mmol/liter) were as follows: placebo, 0.10 ± 0.49 (2.7%); 5 g, 0.65 ± 0.41 (16.3%); 10 g, 0.98 ± 0.36 (22.8%); and 15 g, 1.17 ± 0.47 (27.2%) (p <0.001). Similar changes were observed in total cholesterol and apolipoprotein B concentrations. A dose of 5 g/day of colestipol achieved 51% of the LDL cholesterol reduction noted with 15 g/day. Low-dose colestipol therapy is effective in the treatment of patients with moderate hypercholesterolemia and achieves a proportionally greater reduction in LDL cholesterol than that reported in hypercholesterolemic subjects.

CORONARY ARTERY DISEASE

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Greater Diagnostic Sensitivity of Treadmill Versus Cycle Exercise Testing of Asymptomatic Men with Coronary Artery Disease

Rainer Ph. Hambrecht, Gerhard C. Schuler, Thomas Muth, Martin F. Grunze, Christian T. Marburger, Josef Niebauer, Sabine M. Methfessel, and Wolfgang Kübler

The effect of cycle and treadmill ergometry were compared in 52 asymptomatic patients with angiographically proved coronary artery disease (CAD). The main finding of this study was a significantly higher maximal oxygen uptake, heart rate, rate-pressure product, and extent of stress-induced myocardial ischemia, assessed by thallium-201 scintigraphy. Moreover, there were significantly more patients with signs of myocardial ischemia (positive electrocardiogram or typical angina pectoris, or both) during treadmill exercise compared with cycle ergometry. These findings

suggest that in patients with asymptomatic CAD, treadmill walking seems to be more effective in detecting CAD than cycle ergometry.

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Prognosis in Rupture of the Ventricular Septum After Acute Myocardial Infarction and Role of Early Surgical Intervention

Robert Lemery, Hugh C. Smith, Emilio R. Giuliani, and Bernard J. Gersh

Since 1944, 91 patients (50 men and 41 women, with a mean age 68 years [range 39 to 86]) with ventricular septal rupture after acute myocardial infarction were seen at the Mayo Clinic. Patients were analyzed according to therapy and timing of surgical intervention. Fourteen patients seen before 1965, when surgery was not performed for such a complication or not readily available, were excluded from the analysis. Short-term (30 days) survivors (45%, 35 of 77 patients) were compared with nonsurvivors. With use of logistic regression by univariate analysis, 3 variables were significantly associated with outcome: age (p <0.01), cardiogenic shock (p <0.00001), and long delay between ventricular septal rupture and surgical intervention (p <0.004). By multivariate analysis, however, only cardiogenic shock (p <0.00001) and age (p <0.007) correlated with an adverse outcome. In patients in cardiogenic shock after septal rupture, only those treated surgically within 48 hours survived. The potential for rapid and unpredictable deterioration in the nonsurgical group and the good surgical results warrant early repair for most patients with ventricular septal defect after acute myocardial infarction.

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Prognostic Value of Changes in R-Wave Amplitude During Exercise Testing After a First Acute Myocardial Infarction

Fabrice Leroy, Jean M. Lablanche, Christophe Bauters, Eugène P. McFadden, and Michel E. Bertrand

The prognostic value of exercise-induced changes in R-wave amplitude was investigated in 303 consecutive patients after a first myocardial infarction. R-wave amplitude increased or was unchanged in 159 patients (57.4%) and decreased in 118 (42.6%). Increased R-wave amplitude was related to severity of coronary disease, extent of ST-segment depression on exercise, and time to 1 mm ST depression. During follow-up of 4 ± 1.8 years, 25 patients (9%) died from a cardiac cause, 18 (6.5%) developed infarction, and 32 (11.6%) developed angina. Increased R-wave amplitude had no predictive value for cardiac death or recurrent infarction. The relation between increased R-wave amplitude (p = 0.0001) and the presence of angina at follow-up appears to be related to the presence of more severe underlying coronary disease.

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Effects of Captopril on Left Ventricular Systolic and Diastolic Function After Acute Myocardial Infarction

Carl-Otto Gøtzsche, Peter Søgaard, Jan Ravkilde, and Kristian Thygesen

The effect of captopril on left ventricular systolic and diastolic function in patients with acute myocardial infarction and signs of early left ventricular dysfunction was evaluated in a placebo-controlled double-blind parallel study. Fifty-eight patients were randomized, and 53 completed the 6-

month study period. The left ventricle dilated and diastolic function was increasingly compromized in the placebo group, whereas captopril prevented dilatation of the left ventricle, improved ejection fraction and prevented diastolic dysfunction.

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Acute and Long-Term Outcome of Narrowed Saphenous Venous Grafts Treated by Endoluminal Stenting and Directional Atherectomy

Richard M. Pomerantz, Richard E. Kuntz, Joseph P. Carrozza, Robert F. Fishman, Michael Mansour, Stuart J. Schnitt, Robert D. Safian, and Donald S. Baim

Over a 37-month period, 119 of 176 interventional procedures (68%) performed on saphenous vein grafts (mean age of 8.3 years) were done using either directional coronary atherectomy (n = 35) or Palmaz-Schatz stents (n = 84) rather than conventional angioplasty. Of the remaining 57 saphenous vein graft stenoses treated with conventional angioplasty during this period, 49 (86%) had 1 or more contraindications to stenting or directional atherectomy. There were no emergent coronary bypass surgeries, deaths or Q-wave myocardial infarctions. During the same time period, 50 of 57 vein grafts (88%) were dilated successfully by conventional balloon angioplasty, 3 (5%) of which required emergent coronary bypass surgery. Angiographic follow-up was available in 50 of 64 patients (78%). Restenosis developed in 13 of 50 treated stenoses (26%) (8 of 32 stented grafts and 5 of 18 atherectomy grafts), substantially lower than the restenosis rates previously reported after conventional balloon angioplasty of saphenous vein grafts. These data suggest that most focal stenoses in saphenous vein bypass grafts may be treated safely and effectively using Palmaz-Schatz stenting or directional atherectomy, possibly with better acute and late results compared with those obtained with conventional balloon angioplasty.

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Comparison of Accuracy for Detecting Coronary Artery Disease and Side-Effect Profile of Dipyridamole Thallium-201 Myocardial Perfusion Imaging in Women Versus Men

Barbara A. Kong, Leslee Shaw, D. Douglas Miller, and Bernard R. Chaitman

The relative diagnostic accuracy and prevalence of adverse effects of dipyridamole thallium-201 testing in women were compared with that in male patients. Sensitivity for detection of coronary artery disease was 0.87 in women and 0.94 in men. Specificity was 0.58 in women and 0.63 in men. Sensitivity for detection of 1-vessel disease was 0.60 in women and 0.94 in men (p = 0.001). The sensitivity for detection of multivessel disease (with or without revascularization) was 1.0 and 0.94 in women and in men, respectively. Adverse effects were reported in 62% of women and 38% of men (p = 0.01). There was no significant difference in the incidences of chest pain, headache, nausea, flushing or electrocardiographic changes. The incidences of severe ischemia and dizziness were higher in women.

Reasons for incomplete revascularization were assessed in 618 patients with multivessel coronary artery disease in the 1985–1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry. All significant narrowings ($\geq 50\%$ luminal diameter stenosis) were considered amenable to PTCA in 77% of patients. However, complete correction was intended only for 34%; it was attempted in 28% and successful in 19% of patients. Only 63% of total occlusions were considered amenable to PTCA, and only 54% of those attempted were successfully dilated. PTCA was intended for 38% with 50 to 69% versus 80% with 70 to 89% coronary stenoses and for >85% with narrowings $\geq 90\%$. Thus, incomplete revascularization is frequent after PTCA, and major reasons for incomplete correction include total occlusions that are not PTCA amenable or are unsuccessfully attempted, and less than severe (50 to 69%) coronary narrowings for which PTCA is frequently not intended.

Mortality rates for Medicare patients who had coronary artery bypass surgery were compared with those who had angioplasty or angioplasty and bypass surgery. Data for the study included mortality information on all 96,666 Medicare patients who had bypass surgery or angioplasty in 1985 and detailed clinical information for a sample of 2,362 patients who did not have a myocardial infarction. From the national data set, 30-day and 1-year mortality rates were 3.8 and 8.2% for 25,423 angioplasty patients and 6.4 and 11.8% for 71,243 bypass surgery patients. Mortality rates for the sample of patients were 1.9 and 6.0% for 632 angioplasty patients and 5.1 and 10.8% for 1,730 bypass surgery patients. The risk-adjusted relative risk of mortality for bypass surgery versus angioplasty was 1.72 (p = 0.001) for all patients, 2.15 (p <0.001) for low-risk patients and 0.90 (p = not significant) for high-risk patients. Results suggest that low-risk patients have better survival with angioplasty because of lower short-term mortality.

Moderate exercise was performed for 60 minutes in warm (30.0 ± 0.9°C) and thermoneutral (21.5 ± 0.3°C) environments to evaluate the effect of

heat stress on cardiac performance during work in men with coronary disease. In the warm environment, heart rate was increased (p <0.05) and stroke volume tended to be decreased (p <0.08), with no difference in cardiac output compared with that in the thermoneutral environment. Left ventricular ejection fraction and arterial pressure did not change from minute 6 to 60 of exercise in the warm environment. Arrhythmias were not altered by exercise time or environment. These responses suggest that there is preserved cardiac function in men with uncomplicated coronary disease when performing moderate work in combination with moderate heat stress.

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Mechanisms and Dynamics of Episodes of Progression of 2:1 Atrioventricular Block in Patients with Documented Two-Level Conduction Disturbances

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The mechanisms and dynamics of progression of 2:1 into higher degrees of atrioventricular (AV) block were analyzed during incremental atrial pacing in 7 consecutively studied patients with documented 2-level block. Thirteen episodes were typical because progression of 2:1 AV block was due to previously described mechanisms and with the same dynamics as at the AV node. Seven episodes were atypical because, while atrio-His (AH) Wenckebach periods were occurring: (1) 2:1 increased to 3:1 and then to 4:1 AV block when prolonged His-Purkinje refractoriness coexisted with concealed conduction; (2) 3:2 converted directly to 3:1 block due to block of the next-to-last atrial impulse in the His-Purkinje system during an AH Wenckebach period that terminated with the following atrial impulse; and (3) 4:2 AV block presumably occurred in a transversely dissociated His-Purkinje system. At the AV node or His-Purkinje system the corresponding A(M):V(N) conduction ratios would have indicated different degrees of AV block. This study shows that the phenomenon under consideration, occurring during documented 2-level block could (1) be explained by more mechanisms than previously known, and (2) have dynamics different from those observed at the human AV node or at the His-Purkinje system.

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Electrocardiographic Abnormalities After Radiofrequency Catheter Ablation of Accessory Bypass Tracts in the Wolff-Parkinson-White Syndrome

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Radiofrequency catheter ablation procedures provide a unique opportunity to study electrocardiographic repolarization abnormalities known to occur after the loss of ventricular preexcitation. After ablation of manifest atrioventricular pathways, serial electrocardiograms in 9 of 19 patients demonstrated electrocardiographic abnormalities after the procedure. Seven patients with overt right-sided accessory pathways who also had the

most preexcited QRS complexes demonstrated left superior frontal plane T-wave axis deviation after ablation. Three patients (1 right and 2 left accessory pathways) had conduction abnormalities after ablation that resolved within 18 hours. T-wave changes appeared to be due to the abrupt loss of preexcitation, rather than to injury during ablation.

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Improved Detection of Accessory Pathways That Bridge Posterior Septal and Left Posterior Regions in the Wolff-Parkinson-White Syndrome

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To improve the identification of accessory pathways that bridge the posterior septum and left posterior free wall, coronary sinus maps during atrial pacing and orthodromic supraventricular tachycardia from 21 patients (group I) who needed dissection of both anatomic regions were compared with data from 23 (group II) with pathways confined to the posterior septum and from 9 (group III) with left posterior pathways. The site of earliest ventricular or atrial activation was not helpful alone in distinguishing accessory pathways that bridged both anatomic regions, because 14 of 21 patients (66%) in group I would have been misclassified to either group II or III. In contrast, a new, directional measure of conduction time between adjacent mapping sites over the posterior septal/left posterior junction differed significantly in group I patients compared with in groups II (p <0.01 to <0.0003) and III (p <0.04 to <0.0001) patients. A multivariate model that incorporated the most powerful group differences in directional conduction times improved the identification of group I patients, with a sensitivity of 87% and a specificity of 90%.

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Recordings from the Slow Zone of Reentry During Burst Pacing Versus Programmed Premature Stimulation for Initiation of Reentrant Ventricular Tachycardia in Patients with Coronary Artery Disease

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Programmed premature stimulation and burst pacing were compared for the initiation of ventricular tachycardia (VT) in 16 patients with inducible sustained monomorphic VT. In all patients VT could be induced by programmed premature stimulation with 2 or 3 extrastimuli. On the other hand, initiation of VT by burst pacing was dependent on the length of the train; only 2 to 4 of the 11 trains tested could induce VT in any single patient. Recordings from the slow zone of reentry showed that programmed premature stimulation that induced VT resulted in a critical degree of conduction delay. Similarly, the last beat of a burst pacing train that induced VT was always followed by a similar degree of local conduction delay, whereas trains that failed to induce VT were followed by a lesser delay. In contrast to programmed premature stimulation, burst pacing could initiate, conceal, terminate and reinitiate reentry depending on the length of the train.

Effectiveness of Low-Dose Colestipol Therapy in Patients with Moderate Hypercholesterolemia

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Recommended doses of bile-acid binding resins have an established hypocholesterolemic effect, but data on responses to low doses, especially in women and subjects with moderate hypercholesterolemia, are sparse. A double-blind, placebo-controlled, randomized trial of 3 low doses of colestipol hydrochloride was conducted in women and men with moderate hypercholesterolemia. Men and women with plasma low-density lipoprotein (LDL) cholesterol concentrations >4 mmol/liter (155 mg/dl) and triglyceride concentrations <2.82 mmol/liter (250 mg/dl) were recruited for the study. Eligible patients (54 women and 98 men) were placed on the American Heart Association step I diet 6 weeks before randomization. Participants were subsequently assigned to 1 of 4 drug treatment groups (placebo, and 5, 10 and 15 g/day of colestipol in 2 divided doses) for an additional 12 weeks. Of the 152 patients randomized, 141 completed all aspects of the study. For the treatment groups — placebo, and 5, 10 and 15 g of colestipol — LDL cholesterol reductions (mmol/liter) were observed respectively (n = 141): 0.10 ± 0.49 (2.7%), 0.65 ± 0.41 (16.3%), 0.98 ± 0.36 (22.8%) and 1.17 ± 0.47 (27.2%) (p <0.001). Similar changes were observed in total cholesterol and apolipoprotein B concentrations. The apolipoprotein B/LDL cholesterol ratio increased significantly with increasing colestipol dosage. Modest but insignificant changes in plasma triglyceride levels occurred, and high-density lipoprotein cholesterol levels remained unchanged. A dose of 5 g/day of colestipol achieved 51% of the LDL cholesterol reduction noted with 15 g/day. Low-dose colestipol therapy is effective in the treatment of patients with moderate hypercholesterolemia. The proportionally greater LDL cholesterol reduction in moderate compared with severe hypercholesterolemia was confirmed by examination of the Lipid Research Clinics' Coronary Primary Prevention Trial data set.

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Bile-acid binding resins have been used routinely for the reduction of elevated concentrations of low-density lipoprotein (LDL) cholesterol for >2 decades.[1] Previous investigations using these agents generally studied patients with cholesterol values exceeding the 90th percentile.[2] Patients in these investigations were predominately men, and there are scant data on the effect of bile-acid binding resins in women. The National Cholesterol Education Program (NCEP) Adult Treatment Panel Guidelines recommend drug therapy in subjects with elevated LDL cholesterol and coronary artery disease or ≥2 coronary artery disease risk factors, with the intent of achieving an LDL cholesterol level of 3.36 mmol/liter or considerably lower.[3] Dose response studies of the effect of bile-acid binding resins in hypercholesterolemic patients have been published,[4–9] but there is a paucity of such information in patients with moderate hypercholesterolemia. This investigation examined the effectiveness of low-dose colestipol in patients with moderate hypercholesterolemia who are now targeted as possible candidates for drug treatment by the NCEP Adult Treatment Panel Guidelines.

METHODS

Study design: The investigation was a multicenter, double-blinded, randomized, placebo-controlled study designed to evaluate the effect of 3 low doses of colestipol resin on plasma lipoproteins in subjects with moderate hypercholesterolemia. After an 8-week baseline diet stabilization phase, subjects were randomized into 1 of 4 groups and received either placebo or drug for 12 weeks. Subjects were instructed on a step I diet by reg-

istered dietitians 6 weeks before randomization and requested to maintain the diet recommendations throughout the study. Blood lipid values were obtained at baseline phase weeks 1, 2, 3 and 8, and treatment weeks 4, 8 and 12. Apolipoprotein B values were obtained at baseline phase weeks 2 and 8, and treatment phase week 12. Clinical data and diet compliance information were collected on weekly visits during the baseline 8-week phase and biweekly during the treatment phase.

Subjects: One hundred and fifty-two subjects (54 women and 98 men, mean age 48.9 ± 12 years) with pretrial LDL cholesterol concentrations >4 mmol/liter (155 mg/dl) and triglycerides <2.82 mmol/liter (250 mg/dl) were randomized. Subjects with diabetes, renal insufficiency, thyroid or liver disease were excluded from the trial. The racial composition of the group included 3 blacks, 4 Orientals, 1 Spanish American, 1 other and the remainder Caucasian. Antihypertensive medications were not criteria for exclusion, if blood pressure was stable and the dose was anticipated to be maintained during the trial. Seventeen subjects were receiving β-blocker and 6 diuretic therapy. For the entire group, mean baseline total and LDL cholesterol were 6.26 ± 0.41 and 4.34 ± 0.28 mmol/liter, respectively; the values in women were 6.34 ± 0.40 and 4.33 ± 0.29, and in men 6.18 ± 0.37 (p = 0.01) and 4.36 ± 0.27, respectively. LDL cholesterol was >75th and <90th percentile in both men and women according to the Lipid Research Clinic Prevalence Study.[2] Of 152 subjects randomized, 11 did not complete the study; 7 withdrew for personal reasons (primarily, lack of time) that were unrelated to medication or side effects (placebo, n = 1; 5 g, n = 3; 10 g, n = 1; and 15 g, n = 2), 3 owing to constipation and hiatal hernia symptoms (all in the 10 g group), and 1 owing to infection (placebo). Thus, 141 subjects (92 men and 49 women) completed all phases of the trial. The mean baseline total plasma cholesterol concentration of the 141 subjects (6.26 ± 0.41 mmol/liter) was between the 75th and 90th percentile for white American men aged 45 to 49 years. This range represents a prime target group for treatment according to the new NCEP guidelines.[3] No other lipid lowering drugs were permitted during or for 4 weeks before the study. No subject was treated with probucol in the 6 months before the investigation.

Treatment assignment: Subjects were randomized into 4 groups. Group A received a placebo, and group B a daily dose of 5 g, group C a daily dose of 10 g, and group D a daily dose of 15 g of colestipol. Resin and placebo were prescribed in 2 daily doses to be taken 20 minutes before the morning and evening meals. Drug treatment began after obtaining the blood sample at week 0. Adherence was determined by packet count.

Laboratory methods: Blood samples were obtained after an overnight fast, and plasma triglycerides, and total and high-density lipoprotein (HDL) cholesterol concentrations were determined using methodology developed by the Lipid Research Clinics.[10] LDL cholesterol was calculated using the Friedewald equation.[11] Each of the 3 centers involved in this study determined lipid and lipoprotein values in their respective laboratories. All apolipoprotein B values were determined at a central laboratory at the Medical College of Wisconsin using a rocket gel electroimmunoassay.[12] The coefficient of variation for repeat apolipoprotein B measurement was 5.4%.

Statistical procedures: Analysis of variance was used to determine if there were significant differences among groups at baseline. To determine if the changes in selected variables in response to placebo or drug were significant, the mean of the first 4 values obtained during the baseline (no drug) phase was compared with the mean of the 3 values obtained during the treatment phase after 4, 8 and 12 weeks of therapy using analysis of variance. A 2-sample Student's t test was used to determine significance of the differences in the mean changes between the placebo and individual treatment groups if analysis of variance was significant. Furthermore, analysis of variance with a test for linear trends was used to determine the significance of group changes. Significance was defined at p <0.05.

RESULTS

Baseline: Of 152 subjects randomized, 11 did not complete the study (2 in the placebo group, and 3, 5 and 1 in the 5, 10 and 15 g groups, respectively). Thus, the primary data analyses were performed in groups randomized as follows: placebo, n = 36; 5 g, n = 36; 10 g, n = 33; and 15 g, n = 36. Analysis of variance of group means at baseline indicated no significant intergroup differences in age, body weight or height, or any lipid, lipoprotein or apolipoprotein measurement (Table I). Furthermore, there were no significant intergroup differences when baseline data for all 152 patients randomized and for the 141 completing the trial were analyzed. Using chi-square test for 2-way contingency ta-

bles, no significant differences among medication groups with respect to gender (p = 0.42) or race (p = 0.31) were detected.

Responses to therapy: Stepwise reductions in total and LDL cholesterol were observed for colestipol doses of 5, 10 and 15 g/day. A significant (p <0.001) stepwise reduction in mean total cholesterol from the 4 baseline values compared with the mean values obtained at 4, 8 and 12 weeks of treatment for the placebo and 3 graduated treatment groups were 0.8, −8.1, −13.0 and −17.4%, respectively (Table II and Figure 1); the significant (p <0.001) percent changes for LDL cholesterol in the same groups were −2.4, −14.7, −22.5 and −26.8%, respectively.

Apolipoprotein B measurements were completed in 139 subjects. Percent changes in Apolipoprotein B from baseline (mean of 2 measurements) to 12 weeks of treatment followed a dose response pattern (p <0.06) for the placebo and 3 graduated treatment groups (4.7, 0.8, −4.6 and −12.1%, respectively). The ratio of Apolipoprotein B to LDL cholesterol increased in a significant (p <0.04) stepwise fashion, and mean changes

TABLE II Mean Change Between Baseline Visits (mean of 4 values) and Three Values Obtained During Treatment at 4, 8 and 12 Weeks (mmol/liter; n = 141)

Group (n)	Total Cholesterol	LDL Cholesterol	HDL Cholesterol	Triglyceride	Apo B	Apo B/ LDL Cholesterol
Placebo (36)	−0.05 ± 0.60	−0.10 ± 0.49	−0.02 ± 0.14	0.17 ± 0.31	0.01 ± 0.30	0.02 ± 0.17
5 g (36)	−0.52 ± 0.47	−0.65 ± 0.41	0.03 ± 0.18	0.23 ± 0.33	−0.01 ± 0.29	0.11 ± 0.18
10 g (33)	−0.81 ± 0.34	−0.98 ± 0.36	0.04 ± 0.14	0.28 ± 0.49	−0.06 ± 0.22	0.15 ± 0.15
15 g (36)	−1.08 ± 0.52	−1.17 ± 0.47	−0.01 ± 0.14	0.17 ± 0.42	−0.16 ± 0.27	0.12 ± 0.22

Values are mean ± SE. Significant stepwise reduction in total cholesterol (p <0.00001), LDL cholesterol (p <0.00001), Apo B (p <0.07) and Apo B/LDL cholesterol (p <0.04) (n = 139 for Apo B).
Abbreviations as in Table I.

FIGURE 1. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDLC) concentrations (mmol/liter) at 4 prerandomization visits and 3 post-treatment visits. Stepwise reduction by dose.
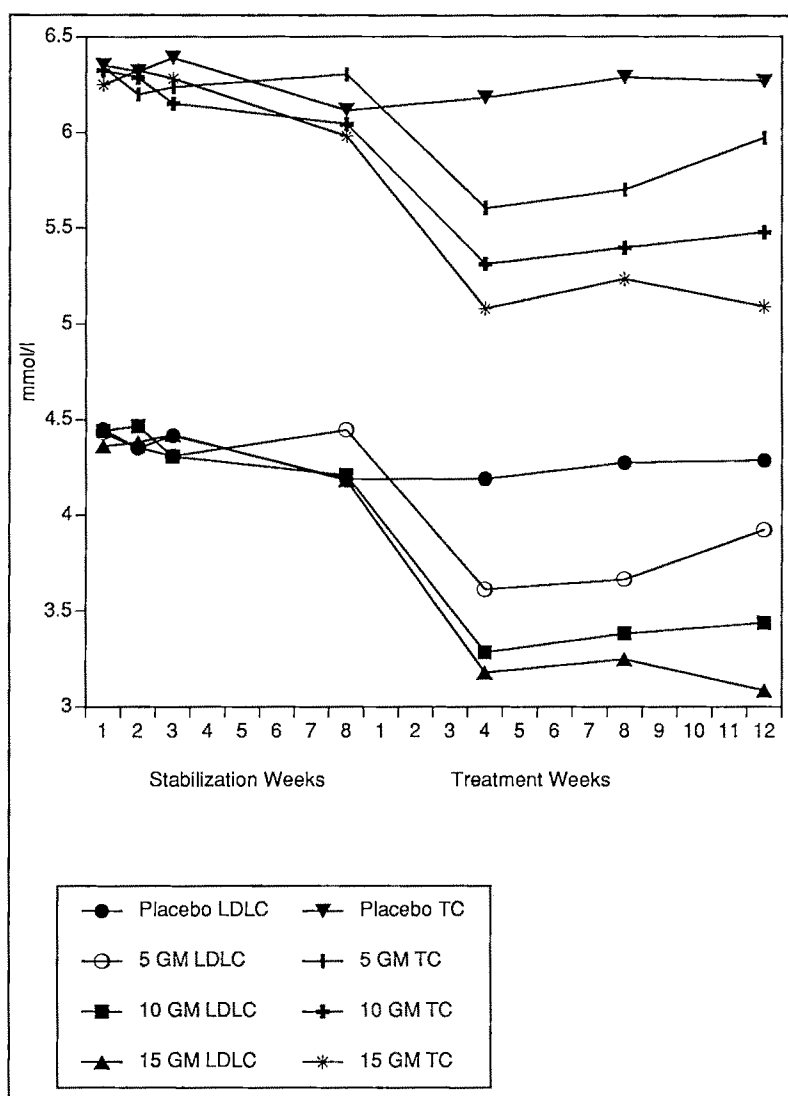
TABLE III Mean Change (mmol/liter) Values in the Four Groups According to Gender

	Triglyceride	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Apo B
Baseline					
Men (n = 93)	1.4 ± 0.5	6.2 ± 0.4	1.2 ± 0.2	4.4 ± 0.3	1.11 ± 0.2
Women (n = 48)	1.3 ± 0.5	6.4 ± 0.4*	1.4 ± 0.3*	4.3 ± 0.3	1.08 ± 0.2
Placebo					
Men (n = 26)	0.12	−0.16	−0.01	−0.19 (−4.5%)	0.01 (5.4%)
Women (n = 10)	0.32	0.23	−0.04	0.12 (3.0%)	0.01 (2.1%)
5 g					
Men (n = 22)	0.19	−0.50	−0.00	−0.59 (−13.1%)	−0.04 (−2.4%)
Women (n = 14)	0.29	−0.54	0.09	−0.75 (−17.2%)	0.05 (5.4%)
10 g					
Men (n = 20)	0.35	−0.69	0.06	−0.91 (−20.6%)	−0.05 (−3.2%)
Women (n = 13)	0.19	−1.00	0.01	−1.09 (−25.5%)	−0.07 (−4.9%)
15 g					
Men (n = 25)	0.20	−1.06	−0.03	−1.12 (−25.5%)	−0.14 (−10.5%)
Women (n = 11)	0.11	−1.15	0.09	−1.28 (−29.8%)	−0.19 (−16.8%)

*p <0.05.
SD values were excluded intentionally, because male and female groups were too small for meaningful statistical analysis. Abbreviations as in Table I.

TABLE IV Studies That Report Dose Effects of Bile-Acid Binding Resins

Study	Resin	Population	No. of Pts. (M/F)	Mean (mmol/liter) Baseline LDL Cholesterol	Mean LDL Cholesterol % Reduction (packet/day)					
					1	2	3	4	5	6
19	Colestipol*	Pediatric FH	26 (18/8)	6.2		15%		12%		
4	Colestipol	Type II	18 (16/2)	5.0				27%		28%
5	Colestipol	Type IIa	23 (19/4)	5.6			20%	23%		26%
6	Colestipol	Type IIa	85 (?)	6.3			22%	24%		27%
7	Cholestyramine	Hyperchol.	16 (4/12)	7.0		27%		33%		
8	Cholestyramine	Hyperchol.	19 (8/11)	7.5	11%	21%		26%		

*Dosage adjusted to 70 kg.
FH = familial heterozygous hyperlipidemia; Hyperchol. = hypercholesterolemia; LDL = low-density lipoprotein.

from baseline for the 2 highest drug doses were also significant.

No significant linear trends were evident for changes in triglyceride (p = 0.84) or HDL cholesterol (p = 0.18) concentrations. Triglyceride values in each dose group

FIGURE 2. Percentage of each group achieving National Cholesterol Education Program Adult Treatment Panel goal (low-density lipoprotein cholesterol <3.36 mmol/liter).

increased significantly from baseline: placebo = +11.9% (p <0.05); 5 g = +16.7% (p <0.05); 10 g = +18.2% (p <0.05); and 15 g = +14.8% (p <0.1). There were no significant differences between groups.

The number of women in each group (placebo, n = 9; 5 g, n = 16; 10 g, n = 13; and 15 g, n = 11) resulted in groups too small to result in meaningful analysis by gender. However, there appeared to be a trend toward greater LDL cholesterol reduction in women (Table III). More importantly, the percent LDL cholesterol reduction achieved by men is consistent with previous investigations in which male subjects were primarily used.[9]

Patients achieving National Cholesterol Education Program goal: Patients who achieved a mean LDL cholesterol <3.36 mmol/liter during the treatment phase were classified as achieving the NCEP LDL cholesterol goal. Of 105 subjects who completed the trial and received colestipol, 46% achieved the NCEP LDL cholesterol goal. The percentage of each dose group achieving this goal increased in a significant (chi-square 46.4; p <0.0001) stepwise manner (Figure 2). Mean LDL cholesterol before colestipol was slightly but significantly (p <0.03) higher in subjects who did not achieve the LDL cholesterol goal (4.40 ± 0.26 mmol/liter) than in those who did (4.29 ± 0.28 mmol/liter).

Diet effect: The dietary intervention was initiated 6 weeks before the drug administration phase. Examina-

tion of lipid values 8 weeks before the drug phase and at week 0 indicate that the mean total and LDL cholesterol values for all 4 dose groups combined (n = 141) decreased by 0.21 mmol/liter (3.4%; p = 0.001) and 0.16 mmol/liter (3.9%; p = 0.003), respectively. Lipid changes in response to the diet were not significantly different among the groups.

Clinical variables: Clinical variables including blood pressure and heart rate at rest, alcohol consumption, and hemoglobin, creatinine and glucose concentrations did not change significantly during the study in any group. Mean change between 6 weeks before and at week 12 of the drug phase in glutamic oxaloacetic transaminase levels were not significant in any group (placebo = −0.8 ± 10 U/liter; 5 g = 2.5 ± 12 U/liter; 10 g = −1.6 ± 25 U/liter; and 15 g = 3.3 ± 9 U/liter). Body weight tended to decrease in a dose-response fashion (p = 0.02) (placebo = −0.32 kg; 5 g = −0.32 kg; 10 g = −0.58 kg; and 15 g = −1.55 kg). Statistical adjustment for changes in weight did not significantly alter the lipoprotein-colestipol dose-response relation.

Side effects: In all, 63 side effects were reported during the course of the study with their frequency being similar among the placebo and active drug groups (placebo = 15; 5 g = 21; 10 g = 14; and 15 g = 13). The most frequently reported side effects were gastrointestinal disturbances (n = 18), but more of these occurred in the placebo (n = 6) than in any of the active drug groups. This is similar to results reported in the Coronary Primary Prevention Trial.[9]

DISCUSSION

Despite the established use of bile-acid binding resins, little information is available regarding lower dose response effects in subjects with moderate hypercholesterolemia and in women. For the treatment of elevated LDL cholesterol, the bile-acid binding resins colestipol and cholestyramine are recommended as agents of first choice.[3] They are prescribed in different absolute weights, but packaged in a manner that allows similar (1 to 6 packets/day) dosing recommendations.

Studies that used a single, moderate to high dose of either 3, 4 or 6 packets/day demonstrated total cholesterol reductions ranging from 12 to 25% and LDL cholesterol reductions from 17 to 32%.[13–17] In these investigations there is a strong correlation (r = 0.64) between the number of packets and mean LDL cholesterol reduction.

Studies that investigated the dose-response issue have tended to concentrate on doses ≥3 packets/day (Table IV). In these studies, the dose of bile-acid binding resins correlated significantly with mean LDL cholesterol reduction, but did not appear to be linear.[4–9] One half of the recommended full dose of 6 packets/day achieves approximately 75% of the LDL cholesterol reduction observed when a full dose is prescribed. These investigations suggest that the greatest response can be achieved at low doses and that high-dose resin therapy contributes progressively less to LDL cholesterol reduction. No previous study investigated the lower dose-response issue in a normal or moderately hypercholesterolemic patient population.

TABLE V One-Year Change (all dose groups) in Low-Density Lipoprotein Cholesterol in the Coronary Primary Prevention Trial

Group	LDL-Cholesterol Quartile	Mean LDL Cholesterol (mmol/L)		
		Baseline	1 Year	% Reduction
Placebo	1	4.39	4.23	3.6%
	2	4.97	4.81	2.8%
	3	5.41	5.28	2.5%
	4	6.38	6.27	1.7%
Cholestyramine	1	4.41	2.91	34.0%
	2	4.97	3.69	25.9%
	3	5.41	4.49	17.0%
	4	6.41	5.69	11.2%
LDL = low-density lipoprotein.				

In the Coronary Primary Prevention Trial,[18] a dose response between self-selected packet count and plasma total cholestrol reduction was demonstrated. A recent analysis of the 1-year LDL cholesterol change in the Coronary Primary Prevention Trial revealed LDL cholesterol reductions in the quartiles that are compatible with the findings in the present investigation (Table V) (i.e., the greatest percent reduction in LDL cholesterol was found in the lowest quartiles).

In our investigation, an LDL cholesterol reduction of 12.3% with diet and the lowest dose of 5 g/day was followed by a significant stepwise further reduction in LDL cholesterol of 7.8 and 4.3% in the 2 higher dose groups compared with that in the control group. The dose of 5 g/day achieved 51% of the LDL cholesterol reduction detected with the 15 g dose. Unlike several previous investigations that used a crossover design, the graded doses in this investigation were not a scheduled dose increase within 1 group; 3 doses were investigated in 3 independent groups. Individual participant dose correlated well with LDL cholesterol reduction (r = 0.67, p <0.001). Triglyceride and HDL-cholesterol concentrations revealed no significant change, which is consistent with previous investigations.[5,16] Our investigation indicates that a substantial amount of the effect of a low-dose regimen in moderate hypercholesterolemia is achieved with the lowest dose used.

Bile-acid binding resin therapy affects LDL particle composition and can result in a smaller, more dense LDL particle with an increase in triglyceride content.[16,20] This is important because lipoprotein size and density may affect the biologic activity of apolipoprotein B and the interaction of the LDL particle with cells.[21] The predominance of smaller LDL subclasses is associated with an increased risk of coronary artery disease.[22] In our investigation, LDL cholesterol reduction was accompanied by relatively less apolipoprotein B reduction that resulted in a significant stepwise increase in apolipoprotein B/LDL cholesterol (p <0.04). Apolipoprotein B/LDL cholesterol change from baseline values was significant for each dose group >5 g (5 g, p = 0.06; 10 g, p = 0.005; and 15 g, p = 0.003). This finding suggests that increasing doses of colestipol result in apolipoprotein B containing lipoproteins that are relatively less cholesterol rich, and this change occurs in a dose-dependent fashion.

The clinical importance of this low-dose investigation is linked to the recent recommendations of the NCEP Adult Treatment Panel guidelines, which recommend that patients with ≥ 2 risk factors for congestive heart disease who do not respond adequately to non-pharmacologic therapy and have LDL cholesterol values >4.14 mmol/liter should be considered candidates for pharmacologic therapy to obtain an optimal LDL cholesterol goal of <3.36 mmol/liter.[3] The present investigation indicates that in subjects with LDL cholesterol values averaging 4.37 mmol/liter and on the American Heart Association step I diet, 5 g/day of colestipol can result in average LDL cholesterol values of 3.73 mmol/liter, 10 g/day can result in values of 3.38 (NCEP Adult Treatment Panel goal), and 15 g/day can result in values of 3.17. In patient populations with known coronary artery disease, a more aggressive approach to LDL cholesterol reduction may be warranted, and in such a population that often has only moderate LDL cholesterol elevation, these findings have enhanced importance.[23-26]

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Greater Diagnostic Sensitivity of Treadmill Versus Cycle Exercise Testing of Asymptomatic Men with Coronary Artery Disease

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Maximal hemodynamic and ventilatory responses using cycle and treadmill ergometer were compared in 52 asymptomatic patients with angiographically proved coronary artery disease. Moreover, test sensitivity with respect to ST-segment depression and typical angina pectoris were compared between exercise modes used. Exercise tests were performed on different days in randomized order. In 42 patients, exercise-induced myocardial ischemia, expressed as a fraction of left ventricular circumference, was assessed by thallium-201 scintigraphy. The main finding of this study was a significantly higher maximal oxygen uptake (1.87 ± 0.4 vs 2.2 ± 0.5 liters/min; p <0.001), heart rate (148 ± 19 vs 158 ± 18 beats/min; p <0.001) and rate-pressure product (28.3 ± 5 · 10^3 vs 30.7 ± 5 · 10^3; p <0.001) during treadmill walking than during cycling. Therefore, stress-induced myocardial ischemia was significantly more extensive after treadmill walking (31 ± 37° vs 45 ± 40°; p <0.001). Moreover, there were significantly more patients with signs of myocardial ischemia (ST-segment depression or typical angina pectoris, or both) during treadmill than during cycle ergometry (35 vs 25 patients; p <0.05). However, lactate levels measured at peak exercise (4.07 ± 2.0 vs 4.38 ± 1.9 mmol/liter) and 3 minutes into the recovery period (5.60 ± 2.2 vs 5.80 ± 2.2 mmol/liter) were comparable between both methods, indicating no significant difference in anaerobic energy production. These findings suggest that walking on a treadmill represents an exercise method with a greater ability than cycling to detect coronary artery disease.

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Maximal myocardial oxygen consumption reached during stress testing for coronary artery disease (CAD) constitutes a crucial factor governing the sensitivity of the particular exercise mode used. Exercise performed on a treadmill is usually associated with greater total body oxygen uptake than bicycle exercise, probably as a result of the greater muscle mass used.[1-5] However, this does not invariably imply a higher level of cardiac work, and therefore the ability to elicit an ischemic response may not be affected.[1,3,6] The purpose of this study was to assess noninvasively differences in total and myocardial oxygen consumption, and in the frequency and severity of stress-induced myocardial ischemia during treadmill and cycle ergometry in asymptomatic patients with angiographically proved CAD.

METHODS

Patients: Fifty-two asymptomatic (Canadian Cardiovascular Society class I to II) male subjects with angiographically proved CAD were recruited for this study. Patients with left main CAD, previous coronary angioplasty or coronary bypass surgery, severely depressed left ventricular ejection fraction (<35%), significant valvular heart disease, and rhythm disturbances (Lown class 4b) were excluded from the study. The study protocol was approved by the ethics committee of the University of Heidelberg. The nature of the study was explained to each subject before written informed consent was obtained.

Exercise tests: Patients were asked to refrain from taking β-blocking agents, nitrates and calcium antagonists for at least 48 hours before the test. After an overnight fasting period, exercise tests were performed on a calibrated, electronically braked cycle in an upright position or on a treadmill on different days in randomized order. On the cycle, work load was increased progressively every minute in steps of 25 W. For the treadmill test, walking speed was kept constantly at 4 km/hour, while the slope was adjusted in 1-minute intervals; elevation was adjusted according to an individualized protocol in order to create comparable steps of approximately 25 W. Exercise was terminated when patients were physically exhausted, developed progressive anginal chest pain, severe dyspnea, or when 3 mm horizontal ST-segment depression was reached. A 12-lead electrocardiogram was recorded every minute using a Mason-Likar lead placement.[7] To ensure accurate blood pressure readings an automatic blood pressure cuff was

	Cycle (n = 52)	Treadmill (n = 52)
HR (beats/min)	104 ± 17	110 ± 15*
SBP (mm Hg)	166 ± 20	167 ± 20
HR × SBP ($\cdot$ 10^3)	17.1 ± 4	18.4 ± 4*
Oxygen uptake (liters/min)	0.91 ± 0.3	1.30 ± 0.3*
CO_2 production (liters/min)	0.78 ± 0.2	1.10 ± 0.3*
Minute ventilation (liters/min)	22.8 ± 6	31.3 ± 8*
Respiratory exchange ratio	0.86 ± 0.1	0.81 ± 0.1*

*p <0.001 versus cycle.
CO_2 = carbon dioxide; HR = heart rate; SBP = systolic blood pressure.

used. There was a significant correlation (r = 0.9; p <0.01) and low intraobserver variability (5%) between systolic blood pressures measured by the conventional cuff method and the automatic cuff system in 20 patients with CAD in our laboratory. The maximal rate-pressure product (double product) was calculated from maximal, simultaneously recorded heart rate and systolic blood pressure during exercise.[8,9]

In 39 patients blood samples were drawn at rest, peak exercise, and 3 minutes into the recovery period from an intravenous catheter placed into an antecubital vein to determine plasma concentrations of lactate and catecholamines.[10]

All electrocardiograms were examined independently by 2 observers, who were unaware of the identity of the patient and the type of exercise test. Discrepancies between the 2 observers were resolved by consensus. ST-segment deviations from baseline were visually measured. The electrocardiograms were categorized as: positive — showing horizontal or downsloping depression ≥1 mm of the ST segment at 80 ms beyond the J point or slowly upsloping ST-segment depression ≥2 mm at 80 ms after the J point in ≥3 consecutive complexes in lead V_4 and/or V_6. Otherwise the electrocardiograms were categorized as negative.[11]

Thallium-201 scintigrams: In 42 patients stress-induced myocardial ischemia was assessed by thallium-201 scintigraphy. While reaching the highest attainable work load, 2 mCi of thallium-201 was injected intravenously, and exercise was continued for another minute at the same or slightly reduced exercise level. Imaging was begun immediately after termination of exercise with the use of a mobile gamma camera (Picker Dyna Mo) equipped with a 7 pinhole collimator. After a 4-hour resting period, redistribution images were conducted in the identical projection. Eight cross-sectional planes through the left ventricular myocardium, perpendicular to the long axis of the left ventricle, were reconstructed from the raw data stored on a magnetic disk using a commercially available computer algorithm.[12,13] In these cross sections the perfusion defects were expressed in degrees of left ventricular circumference. This method was validated comparing findings obtained in vivo with histopathologic data in patients who died during the course of acute myocardial infarction.[14,15] The average of all myocardial cross sections was used for further calculations. The extent of redistribution, a

measure of stress-induced, reversible myocardial ischemia, was assessed by calculating the difference in size between perfusion defects at peak exercise and those at rest. An experienced technician unaware of the patient's identity and the type of exercise test analyzed the thallium-201 scintigrams.

Respiratory gas exchange variables: Respiratory gas exchange data were determined continuously throughout the exercise test using a commercially available system (Jaeger EOS-Sprint). A 30-second gas exchange sampling was used to avoid large variations in gas exchange variables.[16] The following gas exchange variables were analyzed: oxygen uptake (liters/min), carbon dioxide production (liters/min), minute ventilation (liters/min), and respiratory exchange ratio (carbon dioxide production/oxygen uptake). The ventilatory threshold was defined as the oxygen uptake before the systematic increase in the ventilatory equivalent for oxygen without a concomitant increase in the ventilatory equivalent for carbon dioxide.[17] Ventilatory threshold was evaluated in this way by 2 independent observers unaware of the exercise test performed. Interobserver variability and day-to-day reproducibility were determined in our laboratory with 13 healthy male volunteers. In all tests a low interobserver and day-to-day reproducibility (r = 0.95; p <0.001) of 9 and 5%, respectively, were found.[18]

Statistical analysis: Mean value ± SD was calculated for all variables. For statistical evaluation the nonparametric Wilcoxon signed-rank and chi-square tests were used to avoid potential errors from nonnormal distribution of data.[19]

RESULTS

Clinical characteristics: A total of 52 patients (mean age was 56 ± 6 years) were recruited for this study. Thirty-four patients (65%) had previously had myocardial infarction. The mean left ventricular ejection fraction was 57 ± 8%. Nineteen patients (36%) had 1-vessel, 18 patients (35%) had 2-vessel and 15 patients (29%) had 3-vessel disease, defined by ≥50% narrowing among the 3 main branches of the coronary tree. Severity of CAD, assessed by the Gensini score,[20] was 26 ± 18 points. Eighty-seven percent of patients recruited for this study were taking β-blocking agents, 48% calcium antagonists, 42% nitrates, and 14% angiotensin-converting enzyme inhibitors. Patients who underwent thallium testing (n = 42) and patients who did not undergo thallium scintigraphy (n = 10) did not differ with respect to clinical characteristics.

Signs of myocardial ischemia during stress test: Exercise was terminated due to fatigue, leg fatigue or shortness of breath by 46 patients (88%) during cycle ergometry, and by 40 patients (77%) during treadmill exercise. Progressive angina pectoris was the end point in 10 patients (19%) during treadmill exercise, but only in 4 patients (8%) during cycle ergometry. In 2 of 52 patients (4%), both forms of exercise had to be terminated because of asymptomatic downsloping ST-segment depression (≥3 mm). There were diagnostic ST-segment changes in 24 patients (46%) during treadmill exercise, but only in 18 patients (35%) during cycle ex-

ercise. Another 24 patients (46%) reported angina pectoris during treadmill exercise. Only 16 patients (31%) complained of angina pectoris during cycle ergometry. There were significantly fewer patients with signs of myocardial ischemia (positive electrocardiogram or typical angina pectoris, or both) during cycle ergometry than there were during treadmill exercise (25 vs 35 patients; p <0.05).

Ventilatory threshold (Table I): At ventilatory threshold values for oxygen uptake, carbon dioxide production, minute ventilation and heart rate were significantly higher during treadmill than during cycle ergometry (p <0.001). The difference in oxygen uptake at ventilatory threshold between both types of exercise tests was approximately 30%.

Peak exercise (Table II, Figures 1 and 2): During treadmill exercise, maximal heart rate, maximal rate-pressure product, oxygen pulse, oxygen uptake and exercise duration were significantly greater than during cycle ergometry. Consequently, stress-induced myocardial ischemia evaluated by thallium-201 scintigraphy differed significantly between both modes (treadmill 45 ± 40° vs 31 ± 37°, p <0.001). No stress-induced myocardial ischemia could be observed in 8 patients after cycle ergometry, but only 4 of these 8 patients had a negative normal thallium-201 scintigram after treadmill exercise. Repetitive ventricular arrhythmias could not be detected either during treadmill or during cycle ergometry. Individual values for maximal oxygen uptake, heart rate, rate-pressure product and exercise-induced myocardial ischemia during maximal treadmill and cycle ergometry as well as the corresponding correlation

coefficient for each parameter are presented in Figure 2.

Lactate and catecholamines (Table III, Figure 1): Lactate concentrations in plasma measured at rest, peak exercise and 3 minutes into the recovery period were comparable during both forms of exercise.

At peak exercise, patients reached a >20% higher norepinephrine and epinephrine level during treadmill exercise than during cycling (p <0.01).

DISCUSSION

Cycle ergometry has established itself as the predominant method of conducting stress tests in most European countries. Potential advantages may be less up-

TABLE II Hemodynamic and Gas Exchange Variables at Peak Exercise

	Cycle (n = 52)	Treadmill (n = 52)
HR (beats/min)	148 ± 19	158 ± 18*
SBP (mm Hg)	191 ± 22	194 ± 24
DBP (mm Hg)	98 ± 12	91 ± 11
HR × SBP (· 10^3)	28.3 ± 5	30.7 ± 5*
Tl-201 ischemia (degrees)	31 ± 37	45 ± 40*
Oxygen uptake (liters/min)	1.87 ± 0.4	2.20 ± 0.5*
CO_2 production (liters/min)	2.40 ± 0.6	2.58 ± 0.7†
Minute ventilation (liters/min)	78.4 ± 21	82.4 ± 21
Respiratory exchange ratio	1.29 ± 0.2	1.16 ± 0.2*
Ex-time (min)	9.8 ± 3	11.7 ± 3†

*p <0.001 versus cycle ergometry; †p <0.05 versus cycle ergometry.
DBP = diastolic blood pressure; Ex-time = exercise time (minutes); Tl-201 Ischemia = extent of stress-induced myocardial ischemia expressed in degrees of left ventricular circumference (n = 42); other abbreviations as in Table I.

FIGURE 1. During maximal treadmill exercise, oxygen uptake, rate-pressure product and exercise-induced myocardial ischemia, assessed by thallium-201 scintigraphy, were significantly greater than during cycle exercise. No significant difference could be observed for plasma lactate. *p <0.001 vs cycle ergometry; [°], degrees of left ventricular circumference.

	Cycle (n = 39)	Treadmill (n = 39)
Rest		
Lactate (mmol/liter)	1.1 ± 0.4	1.1 ± 0.3
Norepinephrine (nmol/liter)	2.3 ± 1.3	2.0 ± 0.9
Epinephrine (nmol/liter)	0.2 ± 0.1	0.2 ± 0.1
Maximum		
Lactate (mmol/liter)	4.1 ± 2.0	4.4 ± 1.9
Norepinephrine (nmol/liter)	18.0 ± 10.2	22.2 ± 10.9*
Epinephrine (nmol/liter)	1.5 ± 1.2	2.0 ± 1.8*
Recovery (3 minutes)		
Lactate (mmol/liter)	5.6 ± 2.2	5.8 ± 2.2
Norepinephrine (nmol/liter)	15.1 ± 9.3	17.9 ± 8.6*
Epinephrine (nmol/liter)	0.9 ± 0.7	1.2 ± 0.9

*p < 0.01 versus cycle.

per body motion during pedaling, even at very high work loads, compared with walking on a treadmill, resulting in better quality of electrocardiographic tracings. External power can be readily determined during cycle ergometry, which may constitute an important aspect, particularly if the test is conducted for research purposes.

Previous studies have limited the comparison of exercise modes to hemodynamic responses; a few have included electrocardiographic[1,6] or subjective[2] evidence of ischemia. To our knowledge, the present study is the first to use radionuclide techniques to quantify ischemic responses to different modes of exercise. The present results suggest that the drawbacks of treadmill exercise previously described are outweighed by a greater number of patients with any sign of myocardial ischemia (positive electrocardiogram or typical angina pectoris, or both) and a greater extent of stress-induced myocardial ischemia, as demonstrated by thallium-201 scintigraphy.

Several clues to the underlying physiologic mechanisms are apparent: 1. The crucial finding of this study is represented by the significantly higher maximal heart rate (7%) and rate-pressure product (8%) during treadmill exercise compared with cycle ergometry. Thus, treadmill exercise imposes as a greater hemodynamic burden on the myocardium, as indicated by the difference in rate-pressure product, which reliably reflects myocardial oxygen consumption.[8,9] Stress-induced myocardial ischemia depends on the ratio of myocardial oxygen demands and oxygen availability by the coronary system.[7,21] Because of the increased myocardial energy demands in this study, stress-induced, reversible myocardial ischemia during treadmill exercise was approximately 45% higher than it was during cycle ergometry. The sensitivity for detection of CAD with respect to ST-segment depression or typical angina pectoris, or both, was 67% for treadmill and 48% for cycle ergometry in this study (p <0.05).
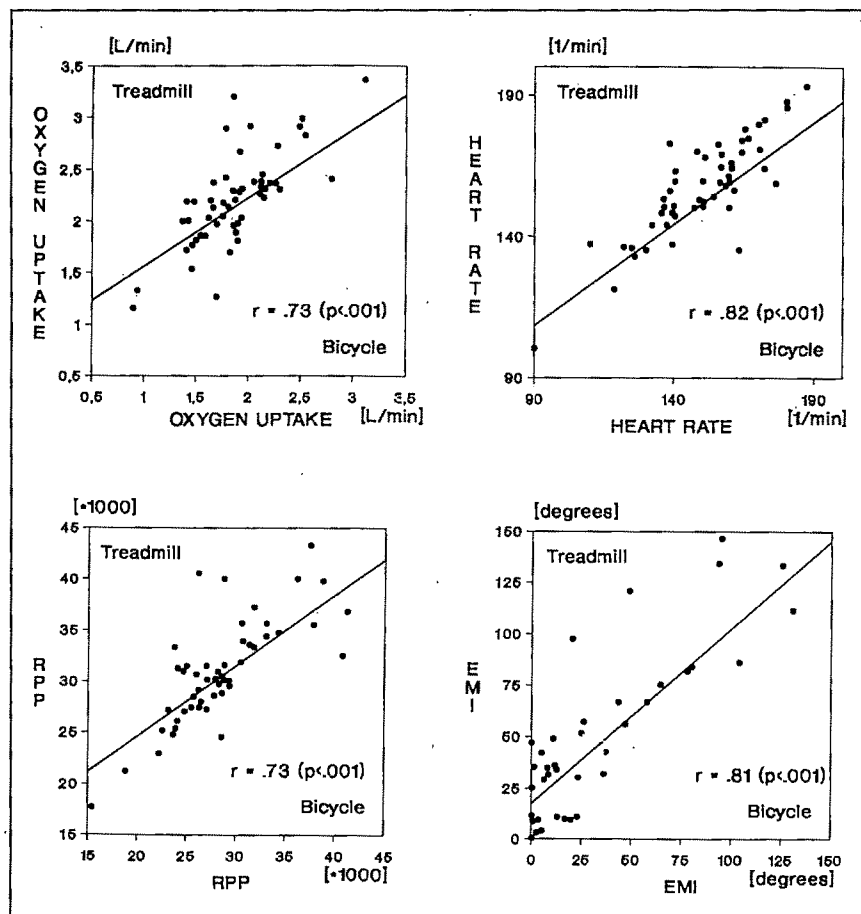
FIGURE 2. Individual values for oxygen uptake, heart rate, rate-pressure product and exercise-induced myocardial ischemia during maximal treadmill ergometry compared with the corresponding values during maximal cycle ergometry. [degrees] = degrees of left ventricular circumference.

2. Comparison between cycle ergometry and treadmill testing has demonstrated that maximal oxygen uptake is 10 to 20% higher when testing with a treadmill. In this study maximal oxygen uptake was approximately 18% greater on treadmill than on cycle ergometer, which is similar to that reported by previous investigators.[1-5]

3. There also is a difference between both modes of exercise in sympathetic drive observed at the end point and in the recovery period. Norepinephrine and epinephrine levels during maximal treadmill exercise exceeded those observed during cycle ergometry by >20%, which may be partly due to a longer duration of treadmill tests.

4. The level at which exhaustion is reached in asymptomatic patients is determined partly by the subject's motivation to endure the discomfort brought about by regional accumulation of lactate as a result of anaerobic metabolism.[22,23] In the present study maximal lactate levels measured at peak exercise and during the recovery period were nearly identical for both modes, indicating no significant difference in anaerobic energy production.

5. Test duration and increments of work load may influence the test result profoundly when comparing 2 different exercise modes.[2,3,24,25] Owing to a greater maximal work load, oxygen uptake and, consequently, test duration during treadmill exercise were higher than during cycle ergometry. As evidenced by the relationship between oxygen uptake and test duration, work rates used in the present study were comparable between both exercise modes (oxygen uptake per minute was 180 and 170 ml/min for treadmill and cycle, respectively).

6. The surprisingly large difference in oxygen uptake at the ventilatory threshold between the 2 exercise modes suggests that oxygen uptake at this threshold can be profoundly influenced by the choice of exercise mode. Therefore, determination of the ventilatory threshold as an index of cardiopulmonary performance may have to take into account the mode of testing.[2,3]

Correlation with previous studies: Although several previous studies[1-5,26-28] have observed higher maximal oxygen uptake, cardiac output and heart rate during treadmill versus cycling, few data are available that compare the sensitivity of both methods in patients with CAD.

Wicks et al[1] found no significant differences in mean ST-segment depression and rate-pressure product between treadmill walking and cycling in 40 patients who had had myocardial infarction. However, marginally more positive treadmill test results were found because of a higher rate-pressure product.

Myers et al,[2] in a study comparing each of 3 different cycle (25 W/stage, 50 W/stage, ramp) and treadmill protocols (Bruce, Balke, ramp), reported that among patients limited by angina pectoris on the treadmill, 26% were limited by leg fatigue during cycle ergometry.

Calvert et al[6] observed in a matched-pairs comparison of 105 patient pairs, matched for sex, age and severity of CAD, comparable sensitivity of both exercise modes using ST-segment depression, angina pectoris, work impairment and impaired blood pressure response as parameters suggesting CAD.

Study limitations: There are several limitations of this study that deserve comment: When limited-angle tomography with an angle aperture of <180° (i.e., 7-pinhole tomography) is used for detecting stress-induced myocardial ischemia, 2 inherent problems due to a diminished z-axis resolution are concealed: (1) an overrepresentation of apical cross sections compared with cross sections closer to the base of the heart; and (2) a propagation of perfusion defects into cross sections regularly not involved by myocardial ischemia. However, in this study each patient represented his own control, and because there is a high reproducibility of 7-pinhole recordings,[29] these technical limitations appear negligible and should not have affected the validity of the results.

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Prognosis in Rupture of the Ventricular Septum After Acute Myocardial Infarction and Role of Early Surgical Intervention

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Since 1944, 91 patients (50 men and 41 women, mean age 68 years [range 39 to 86]) with ventricular septal rupture after acute myocardial infarction were seen at the Mayo Clinic. Patients were divided into 4 groups according to therapy and timing of surgical intervention. Fourteen patients seen before 1965, when surgery was not performed for such a complication or not readily available, were excluded from the analysis. Group 1 (n = 22) had surgery within 48 hours of septal rupture, group 2 (n = 6) underwent operation between 2 and 14 days, group 3 (n = 24) had surgery after 14 days, and group 4 (n = 25) only received medical treatment. Short-term (30 days) survivors (45%, 35 of 77 patients) were compared with nonsurvivors. Using logistic regression, by univariate analysis, 3 variables were significantly associated with outcome: age (p <0.01), cardiogenic shock (p <0.00001), and long delay between ventricular septal rupture and surgical intervention (p <0.004). By multivariate analysis, however, only cardiogenic shock (p <0.00001) and age (p <0.007) correlated with an adverse outcome.

In patients with cardiogenic shock after septal rupture, the prognosis was uniformly fatal unless patients undergo early surgery. None of the 23 patients in groups 2, 3 or 4 survived, whereas 5 of 13 patients (38%) who had surgery within 48 hours of septal rupture survived. In patients with congestive heart failure, the long-term outcome was similar among patients who underwent early surgery; 3 of 6 patients (50%) survived compared with 8 of 15 patients (53%) in whom surgery was delayed. In group 4 patients (no surgery), 12 of the 19 patients who were nonsurvivors were in cardiogenic shock and died within 48 hours of septal rupture, but in the remaining 7 patients, death occurred between 3 and 9 days in 5 patients, and at 20 and 30 days in 2 others. Thus, in patients with cardiogenic shock after septal rupture, only those who underwent operation within 48 hours survived; the potential for rapid and un-
predictable deterioration in the nonsurgical group and the good surgical results warrant early repair for most patients with ventricular septal defect after acute myocardial infarction.

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Rupture of the ventricular septum is an infrequent but often fatal complication of acute myocardial infarction.[1,2] Congestive heart failure or cardiogenic shock is the usual clinical presentation. Afterload reducing agents and intraaortic balloon counterpulsation are only supportive measures; closure of the ventricular septal defect is necessary in nearly all patients, although the timing of the operation has been a subject of considerable debate.[3-7] The prognosis of patients with acute septal rupture has been reported to be influenced by the site of the myocardial infarction[8] and by the presence or extent of right ventricular dysfunction.[8-10] In the present study, we reviewed the clinical features and course of patients with septal rupture seen during the last 5 decades at the Mayo Clinic hospitals. Our report focuses on short- and long-term survival in relation to (1) clinical and hemodynamic characteristics of the patient at the time of diagnosis of the septal rupture and, (2) the use and timing of surgical repair.

METHODS

Since 1944, 91 patients with a postmyocardial infarction–related ventricular septal defect were diagnosed at the Mayo Clinic. The cases were identified by a computer search of medical records, and some have been included in earlier reports.[4,9,11] Only patients whose ventricular septal defect was found by echocardiography or confirmed by cardiac catheterization, operation or autopsy were selected for analysis.

Diagnostic procedure: The diagnostic procedures included right-sided cardiac catheterization in 64 patients, coronary angiography in 30 patients, and left ventriculography in 47 patients. The diagnosis of ventricular septal defect was confirmed by a right atrium-to-pulmonary artery step-up in oxygen content at cardiac catheterization in 60 patients, by quantification of a shunt during radionuclide angiography or by 2-dimensional echocardiography only in 4 patients, by direct surgical observation in 5 patients, and by autopsy in the remaining 22. The pulmonary-to-systemic flow ratio and percentage of shunt were calculated using the standard formula. Hemodynamic support by intraaortic balloon

TABLE I	Extent of Coronary Artery Disease		
No. of Coronary Arteries Narrowed > 70%	Number of Patients		
	By Angiography* (n = 30)	By Autopsy (n = 37)	Total (%)† (n = 67)
1	20	16	36 (54)
2	2	7	9 (13)
3	7	9	16 (24)
0	1	5	6 (9)

*Angiographic evidence of collateral vessels in 20%.
†Both angiography and autopsy in 5 patients.

counterpulsation was used (since 1977) in 20 patients. Streptokinase was administered to 2 patients.

Definitions: Cardiogenic shock was defined as persistent hypotension (systolic blood pressure ≤90 mm Hg) associated with evidence of inadequate organ and peripheral perfusion. The Killip classification[12] was used to divide patients into those with mild, moderate or severe congestive heart failure (Killip class I, II and III). Short-term survival was defined as 30 days or hospital survival after operation in the surgical group and 30 days or hospital survival after the diagnosis of septal rupture in the medical group.

Follow-up: Follow-up information regarding subsequent medical events and overall clinical status was obtained for all patients from the medical records or by communication with the patients, their families or their physicians. The results of autopsy were available for 37 of the 76 patients who died.

Statistical analysis: The unpaired t test was used to compare continuous variables. Statistical significance was defined as p <0.05. Individual and multiple independent variables correlating with mortality within 30 days after the septal rupture or with long-term survival were identified by using the logistic multiple regression procedure[13] and the Cox regression model.[14] This method of analysis was applied only to patients seen after 1965, because before this date, surgery was either not

performed for septal rupture or was not readily available. The nonparametric Kaplan-Meier method was used to calculate actuarial survival rates.[15]

RESULTS

Clinical characteristics: The 91 patients (50 men and 41 women) were aged 68 years [range 39 to 86]). Fifty (55%) had been admitted to another hospital initially and then referred to a Mayo Clinic hospital for further treatment. Myocardial infarction was anterior in 49 and inferior (or inferoposterior) in 42 patients. At autopsy, a recent circumferential nontransmural infarction was identified in 1 case diagnosed clinically as anterior infarction. A history of hypertension was recorded in 41% of the patients, of preceding angina in 29%, and of a previous myocardial infarction in only 14%. Diabetes mellitus was recorded in 14 patients (insulin-dependent in 3); 51% of the patients had a history of cigarette smoking.

A new systolic murmur was present in all patients who had a clinical diagnosis of postmyocardial infarction-related ventricular septal defect; a thrill was recorded in 51% (37 of 72 patients). Complete heart block was seen in 5 patients with an inferior myocardial infarction and in 2 patients with an anterior myocardial infarction. A bundle branch block or an intraventricular conduction defect developed in 14 patients, and atrial tachyarrhythmias occurred in 13 patients.

The time interval between the onset of myocardial infarction and the diagnosis of septal rupture was 1 week or less in 77 of 86 patients (89%). However, the mean ± SD interval was 2.2 ± 2.1 days in those with an inferior myocardial infarction and 6.2 ± 11 days in patients with an anterior myocardial infarction; this was the only variable that was significantly different (p <0.01) between patients with anterior and those with inferior infarctions.

Extent of coronary disease: The extent of coronary artery disease is shown in Table I. More than half of the patients had 1-vessel coronary artery disease (≥70%
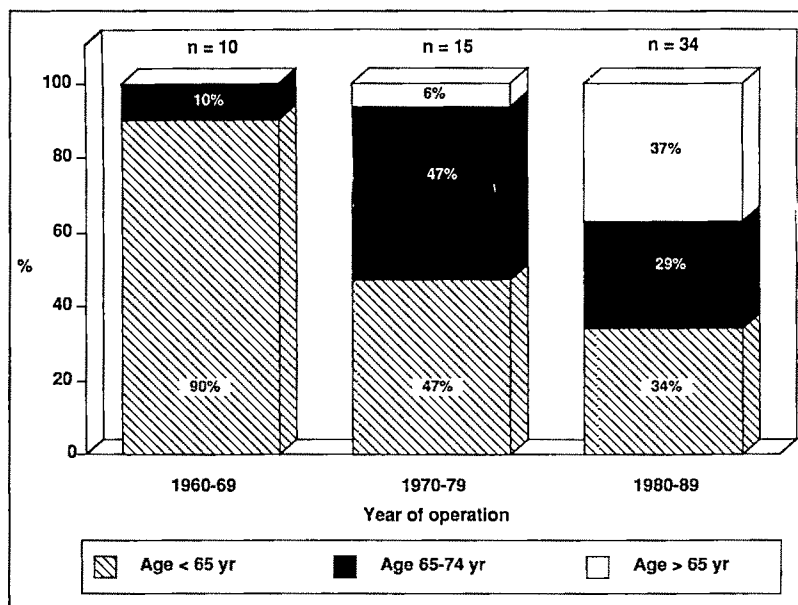
FIGURE 1. Relation between the year of surgical closure of septal rupture and the age of the patients. As shown, before 1970 none of the patients treated surgically were aged ≥75 years; only 6% of these patients are included in the surgical series between 1970 and 1979. However, since 1980, 37% of patients who had surgery were ≥75 years. By multivariate analysis, older age was an independent predictor of adverse outcome.

narrowing of the luminal diameter), but collateral vessels to the infarct area were present in only 20% of the patients who underwent coronary angiography. In 1 patient with a prior history of hypertension and who experienced a septal rupture 5 days after an anterior myocardial infarction, a significant stenosis of only the first septal perforator branch was documented at coronary angiography. Recanalization, coronary spasm or other factors may explain the absence of significant coronary disease in these 6 patients.

Year of surgery: Figure 1 shows the age of the patients according to the year of operation. There were no patients aged >75 years who underwent operation between 1960 and 1969. Since 1980, this age group comprises 37% of the total amount of patients undergoing operation. The first surgical correction of postmyocardial infarction–related ventricular septal defect at the Mayo Clinic was performed in 1960; the first such surgical repair done within 48 hours after rupture was in 1975. In the 8 years between 1980 and 1988, 30 of the 38 patients (79%) were treated surgically, and 70% of these operations were performed within 48 hours after rupture. Of the 8 patients who did not undergo surgery during this time interval, 6 were in cardiogenic shock; severe noncardiac disorders precluded operation in 2 pa-

tients, 3 died within 24 hours after rupture, 1 died 4 days after rupture (patient was in Killip class II) and operation was deferred in 2.

Survivors versus nonsurvivors: The patients were divided into 4 groups according to the type and timing of therapy (Table II). Fourteen patients seen before 1965 are not included in the analysis because surgical repair for this complication before that time was either unavailable or seldom performed. Medical treatment >20 years ago was also extremely limited; for the purpose of survival analysis, this study therefore focused on patients seen after 1965. Group 1 includes 22 patients surgically treated within 48 hours after the diagnosis of ventricular septal defect; group 2 includes 6 patients (5 in cardiogenic shock) surgically treated between 2 and 14 days after the diagnosis (3 days in 1, 4 days in 3, 5 days in 1 and 7 days in 1); group 3, 24 patients who underwent operation >14 days after the diagnosis (mean interval between septal rupture and operation, 9.9 months [range 0.6 to 70]); and group 4, 25 patients who only had medical treatment.

Hemodynamic profile (Table III): There was no significant difference in hemodynamic variables between anterior and inferior infarctions. Table I lists the hemodynamic values obtained in 30-day survivors and non-

FIGURE 2. Long-term survival in 30-day survivors after postmyocardial infarction–related ventricular septal defect with surgical intervention or medical therapy. Group 2 (not shown) includes only 1 patient (who survived >5 years). Numbers in parentheses indicate the number of patients at the beginning of each interval.
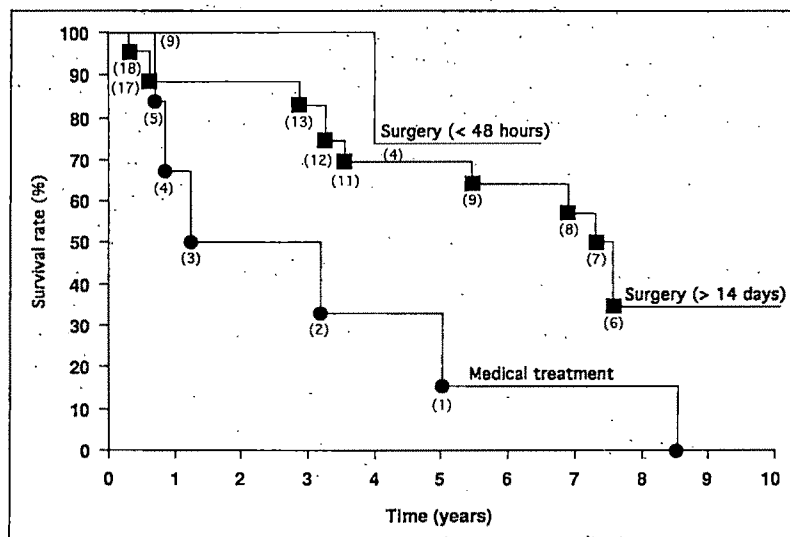
survivors; there was no significant difference between both groups of patients. Serum creatinine was 1.5 ± 0.6 in patients who survived 30 days compared with 2.1 ± 1.3 in nonsurvivors (p = not significant). For the entire group of patients, the greater number of patients with congestive heart failure (53%) may reflect a referral bias, because patients with cardiogenic shock may have been treated or died at their primary hospitals.

Short-term survival: Thirty-day survival (Table II) in group 1 patients was 41% (9 of 22 patients). Five of these patients (59%) were in cardiogenic shock before operation. Only 1 of the 6 patients in group 2 was not in cardiogenic shock and was the only patient to survive 30 days. In group 3, only 2 of the 24 patients had cardiogenic shock and both died; overall survival in this group was 79%.

Of the 25 patients in group 4, only 6 (24%) were 30-day survivors (none of whom were in cardiogenic shock). Sixteen of the 19 patients (84%) were in cardiogenic shock; 12 of these patients (63%) died within 48 hours of septal rupture, and none were 30-day survivors. By univariate analysis, short-term survival was significantly associated with: (1) the absence of cardiogenic shock (p <0.00001), (2) age (p <0.01) (the average age of survivors was 64 ± 11 years compared with 71 ± 10 years in nonsurvivors), and (3) a long delay between septal rupture and surgical closure or hospital admission (the average delay in survivors was 75 ± 149 days compared with 9 ± 27 days in nonsurvivors). However, by multivariate analysis, delay of surgery was not an independent predictor of outcome. Only cardiogenic shock (p <0.00001) and age (p <0.007) were significantly associated with short-term outcome.

Long-term survival (Figure 2): The 5-year cumulative survival in 30-day survivors was 75% in group 1, 70% in group 3 and 14% in group 4; there was one 30-day survivor in group 2 patients and this patient died during follow-up. Univariate and multivariate analyses of long-term survival in 30-day survivors did not demonstrate any independent predictors of long-term survival.

In group 4 (only medical treatment), death after 30 days occurred at 10, 12, 35, 61 and 87 months. All of these patients had congestive heart failure on admission but were not in shock. The remaining patient in this group, a 71-year-old woman, refused surgical treatment; she had congestive heart failure with a significant left to right shunt (QP/QS = 2.7), 3-vessel coronary artery disease and a posterolateral aneurysm. She died suddenly 8.5 years later.

Of the twenty-nine 30-day surgical survivors, 2 underwent repeat operation for recurrence of ventricular septal defect and 1 of these died perioperatively. Of the 20 deaths during follow-up (up to 16 years), 7 were sudden cardiac death.

DISCUSSION

The evolution in the management of postmyocardial infarction–related ventricular septal defect during the last 4 decades is illustrated in this large series from a single institution. Our data support recent studies showing that: (1) early surgical intervention improves short-

and long-term survival, especially in patients in cardiogenic shock[3,6,16–18]; and (2) age is an independent predictor of adverse outcome.[19–21]

Site of myocardial infarction: In patients who have postmyocardial infarction–related ventricular septal rupture, the characteristic triad includes a history of prior hypertension[22] (41% in our series), first myocardial infarction[22] (86% of our patients), and 1-vessel coronary artery disease or no significant coronary stenosis (54% in our series) with minimal collateral formation to the infarcted area.[19,22,23] Although several studies have shown an increased surgical mortality in patients with inferior infarction,[5,6,8,24] we and others[20,25] have not documented this finding. Anterior infarctions were seen in 53% of our patients, and the only significant difference between anterior and inferior infarctions was the longer delay between anterior myocardial infarction and septal rupture.

Right ventricular dysfunction: Right ventricular dysfunction has been proposed as a major pathophysiologic mechanism underlying cardiogenic shock in acute ventricular septal rupture and is an adverse prognostic factor.[8–10] We did not demonstrate any significant hemodynamic differences between survivors in comparison with nonsurvivors. This could be related to the relative insensitivity of right atrial pressure as a marker of right ventricular dysfunction. Most of our patients were seen during a period when accurate evaluation of right ventricular function was unavailable. Furthermore, the aggressive approach of early surgery in 22 of our patients may have resulted in more survivors in some of these patients who otherwise would have died.

Congestive heart failure and cardiogenic shock: The clinical course of patients with postmyocardial infarction–related ventricular septal defect is closely related to the presence or absence of cardiogenic shock. In our series, early surgery was associated with a short-term survival of 38% (5 of 13) in patients who presented with cardiogenic shock, compared with 0% (0 of 23) in the remaining patients who underwent delayed surgery or who were treated medically.

Patients with cardiogenic shock after septal rupture thus represent one of the most serious complications following myocardial infarction, and only urgent measures will improve survival: immediate institution of intraaortic balloon counterpulsation and prompt surgical closure of the septal defect appear to offer the only realistic opportunity for survival, since the mortality with medical therapy alone or among patients undergoing delayed surgery was 100%. This analysis is subject to bias because in part the universal mortality among patients treated medically comprises patients who died before operation, even if this option was under consideration. Nonetheless, the argument is persuasive that in patients with acute interventricular septal rupture and cardiogenic shock, the only chance for survival is emergency surgery.

In patients with congestive heart failure, surgery may be delayed and patients should be stabilized and well prepared for surgery.[19] The potential for rapid deterioration in those awaiting surgery suggests that these

patients need optimal care and surgery should be performed during their hospitalization, preferably during the first or second week after septal rupture.

Age: Although none of the patients in our series who underwent surgery before 1960 were >75 years, this group comprises 37% of patients treated surgically since 1980. Older patients with more widespread multisystem failure are at a greater risk, and will constitute a major challenge in the management of septal rupture in the next decade.[19,21,26]

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Prognostic Value of Changes in R-Wave Amplitude During Exercise Testing After a First Acute Myocardial Infarction

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To investigate the prognostic value of exercise-induced changes in R-wave amplitude and their relation to other exercise and angiographic variables, 303 consecutive patients who underwent maximal exercise testing and coronary angiography within 2 months of a first acute myocardial infarction were studied. R-wave amplitude at peak exercise increased or was unchanged in 159 patients (57.4%) and decreased in 118 (42.6%). Increased R-wave amplitude was significantly related to underlying 3-vessel disease (p = 0.0001), the extent of ST-segment depression on exercise (p = 0.0001), and the time to 1 mm ST depression (p <0.05). Follow-up information was available in 285 patients (86.4%) at a mean of 4 ± 1.8 years. Death from cardiac causes occurred in 25 patients (9%); 18 (6.5%) developed recurrent myocardial infarction, and 32 (11.6%) developed angina. Variables with a predictive value for cardiac death were maximal exercise heart rate (p = 0.0005), occurrence of exercise-related supraventricular arrythmia (p = 0.02), and number of diseased vessels (p = 0.02). R-wave changes had no predictive value. No variable had a predictive value for recurrent infarction. Maximal exercise heart rate (p = 0.02) and increased R-wave amplitude (p = 0.0001) were significantly related to the occurrence of angina at follow up. Exercise-related R-wave increases were associated with the presence of angina at follow-up, but had no predictive value for cardiac death or recurrent infarction; their association with subsequent angina appears to reflect an association with more severe underlying coronary disease.

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Exercise testing has been shown to be useful in identifying subgroups of patients with an increased risk of subsequent cardiac events after an acute myocardial infarction.[1,2] Previous studies suggested that the analysis of changes in R-wave amplitude during exercise in these patients may provide additional prognostic information; however, whereas 1 study suggested that an exercise-induced decrease in R-wave amplitude was an adverse prognostic factor, another suggested the converse.[3,4] This study was designed to assess the prognostic significance of changes in R-wave amplitude during exercise testing after a first myocardial infarction and to determine whether there was a relation between these changes and the occurrence of cardiac death, recurrent myocardial infarction or angina pectoris during follow-up. Furthermore, we compared the predictive value of R-wave changes with those of other exercise test variables and the angiographic findings.

METHODS

Patients: We identified 303 patients who (between October 1978 and December 1983) presented with a first documented acute myocardial infarction and underwent both exercise testing and coronary angiography within 2 months of discharge. The diagnosis of acute myocardial infarction was based on history of prolonged ischemic pain (>30 minutes) associated with new Q waves or ST-T–segment changes and a significant (>twofold) increase in creatine kinase levels. The site of infarction was anterior in 28% and inferior in 47%; 25% were non-Q-wave infarcts. From this initial cohort, follow-up information was available in 285 patients. Documented noncardiac death occurred in 8 of this group during follow-up, and these patients were excluded. The remaining 277 patients are the subject of this report.

Exercise testing: Treadmill exercise testing was performed with a computerized system (CASE 2, Marquette Electronics) when antianginal medication had been discontinued for >48 hours. The Bruce protocol was used in all exercise tests.[5] A Mason-Likar modified 12-lead electrocardiogram was recorded before exercise, at the end of each stage, at peak exercise and 8 minutes after exercise. The level and slope of the ST segment were continuously recorded in 3 electrocardiographic leads (V_2, V_5 and aVF). ST-segment depression was considered significant if ≥1 mm of horizontal or downsloping ST-segment depression measured 60 ms after the J point of the electrocardiogram developed com-

pared with that at baseline. Exercise was discontinued at the patient's request if incapacitating fatigue, dyspnea or increasing angina occurred. Other end points were decrease (>10 mm of mercury) in systolic blood pressure, occurrence of ventricular tachycardia or frequent premature ventricular contractions, and development of a marked ST-segment depression (>3.5 mm).

R-wave amplitude measurements: The RS criterion used in this study was the sum of the R wave in V_5 plus the S wave in V_2 (mm). These measurements were obtained from computer-averaged electrocardiograms obtained at baseline and peak exercise. The computer average was the mean of 25 consecutive beats. Patients were classified into the following 2 groups depending on the R-wave response to exercise: those in whom R-wave voltage decreased during exercise (normal response), and those in whom it increased during exercise or remained unchanged (abnormal response). Measurements were obtained by an observer unaware of the results of angiography.

Angiography: Coronary angiography was performed in multiple projections within 9 days of exercise testing using the Judkins technique. Single-plane left ventriculography was performed in a 30° right anterior oblique projection. Angiograms were reviewed by 2 experienced cardiologists. Patients were classified as having 1-, 2- or 3-vessel coronary disease depending on the number of arteries with significant (>50% reduction in luminal diameter) stenoses. Left ventricular volumes and ejection fraction were determined using the area-length method modified for single-plane calculation. The outline of the ventriculogram was divided into 3 segments (anterior, apical and inferior), and the contraction in each segment was classified as normal, hypokinetic, akinetic, dyskinetic or aneurysmal.

Follow-up: We obtained follow-up data by mail or telephone contact with the patient and general practitioner in 70% of cases; follow-up data was obtained from the patient alone in 12% and from the general practitioner alone in 18%. We ascertained whether patients were alive, had developed a further acute myocardial infarction or had angina. Only patients with anginal symptoms corresponding to at least class 2 of the Canadian Cardiovascular Society classification were considered to have angina pectoris.

Statistical analysis: Differences between groups in the rates of cardiac death, and recurrent myocardial infarction and angina pectoris during follow-up were assessed with the log-rank test. The correlation between R-wave changes and other exercise test or angiographic variables was assessed for continuous variables with Student's t tests and for discrete variables with chi-square analysis. A stepwise discriminant analysis was used to determine whether exercise-induced changes in R-wave amplitude were an independent predictor of events during follow-up (death, recurrent myocardial infarction or angina pectoris).

RESULTS

Follow-up results: Follow-up information was available for a mean of 48 ± 22 months. Baseline character-

TABLE I Clinical Characteristics of Patients Related to R-Wave Amplitude Changes

	R-Wave Decrease (n = 118)	R-Wave Increase (n = 159)	p Value
Age (yr ± SD)	48.2 ± 9.5	49.4 ± 9.2	NS
Men (%)	96	93	NS
Systemic hypertension (%)	24	23	NS
Cigarette smokers (%)	78	76	NS
Diabetes mellitus (%)	14	5	<0.05
Hypercholesterolemia (%)*	44	41	NS
Anterior AMI (%)	45	15	<0.0001
Inferior AMI (%)	33	59	<0.0001
Non-Q-wave AMI (%)	22	26	NS
Killip class > 1 (%)	8	4	NS

*Cholesterol > 2.5 g/L.
AMI = acute myocardial infarction; NS = not significant.

TABLE II Exercise Test and Angiographic Variables Related to R-Wave Amplitude Changes

	R-Wave Decrease (n = 118)	R-Wave Increase (n = 159)	p Value
Exercise duration (min)	8.4 ± 2.6	7.8 ± 2.6	NS
Maximal heart rate (beats/min)	150 ± 26	144 ± 23	<0.05
Maximal systolic blood pressure (mm Hg)	182 ± 29	181 ± 30	NS
Maximal ST depression (mm)	0.6 ± 0.9	1.2 ± 1.1	0.0001
Time to 1 mm ST-segment depression (min)	5.6 ± 2.6	4.6 ± 2.7	<0.05
Angina during exercise (%)	8	22	0.002
Ventricular arrythmias (%)	19	26	NS
Supraventricular arrythmias (%)	5	3	NS
Number of narrowed coronary arteries (%)			0.0001
0	14	7	
1	39	36	
2	36	27	
3	11	30	
Ejection fraction (%)	52 ± 13	53 ± 11	NS
End-diastolic volume (ml)	108 ± 26	108 ± 28	NS
Wall motion abnormalities (%)	65	65	NS

NS = not significant.

istics of the study population are presented in Table I. During this period there were 25 cardiac-related deaths (9%) of which 14 (56%) were sudden. Seventeen deaths (68%) occurred within 3 years of the index infarction. During the same period, 18 patients (6.5%) had a recurrent myocardial infarction and 32 (11.6%) developed angina. Functional status could not be assessed in 27 patients.

Exercise test and angiographic variables related to R-wave amplitude changes: Table II shows the exercise test data and angiographic findings in the 2 groups. In patients in whom R-wave amplitude increased or remained the same, the magnitude of ST-segment depression at peak exercise was significantly higher and the extent of coronary disease was significantly greater. Furthermore, significant ST-segment depression appeared earlier in this group who more often developed angina during the test, and maximal heart rate achieved was slightly but significantly lower. Mean exercise du-

TABLE III Incidence of Coronary Events in Patients Who Achieved a Heart Rate > or < 130 Beats/Min Related to Changes in R-Wave Amplitude

	R-Wave Decrease Heart Rate (beats/min)		R-Wave Increase Heart Rate (beats/min)		
	<130 (n = 28)	>130 (n = 90)	<130 (n = 51)	>130 (n = 108)	p Value
Cardiac death (%)	6 (21.4)	8 (8.9)	6 (11.8)	5 (4.6)	NS
Recurrent AMI (%)	4 (14.3)	5 (5.6)	5 (9.8)	4 (3.7)	NS
Angina (%)*	3 (10.7)	4 (4.9)	11 (21.6)†	14 (13.5)†	<0.05†

*Functional status could not be assessed in 27 patients.
†For comparison with R-wave decrease.
Abbreviations as in Table I.

TABLE IV Comparison of Predictive Value of Changes in R-Wave Amplitude with That of Other Variables: Results of Discriminant Analysis

End Point	Variables	p Value
Cardiac death	Maximal heart rate	0.0005
	Supraventricular arrhythmias	0.02
	No. of diseased vessels	0.02
	Changes in R-wave amplitude	NS
Recurrent infarction	Changes in R-wave amplitude	NS
Angina	Changes in R-wave amplitude	0.0001
	Maximal heart rate	0.02

NS = not significant.

ration and ejection fraction, and the extent of left ventricular wall motion abnormalities were similar in both groups.

Changes in R-wave amplitude: relation to events during follow-up: Table III shows the incidence of coronary events related to changes in R-wave amplitude. The results are presented according to maximal heart rate achieved during exercise, because it has been suggested that changes in R-wave amplitude may be dependent on heart rate.[6] There was no significant difference in the incidence of cardiac death or recurrent infarction between the groups. However, the percentage of patients who had angina at follow-up was significantly higher in those in whom R-wave amplitude increased or remained unchanged (p <0.05). These findings were independent of the maximal heart rate achieved on exercise.

Changes in R-wave amplitude: predictive value compared with that of other variables: Table IV shows the predictive value of changes in R-wave amplitude compared with that of other variables. Maximal heart rate achieved during exercise was the best predictor of cardiac death after myocardial infarction, followed by the occurrence of supraventricular arrhythmias during exercise and the number of diseased vessels. However, changes in R-wave amplitude had no predictive value for cardiac death. No variable tested had a significant predictive value for recurrent myocardial infarction.

Increased R-wave amplitude during exercise was significantly (p <0.0001) associated with the occurrence of angina during follow-up. This predictive value was independent of that of other variables, and only the maximal heart rate achieved provided additional information.

DISCUSSION

The results suggest that the analysis of changes in R-wave amplitude during exercise testing after a first acute myocardial infarction helps to identify patients who will subsequently develop angina pectoris, but is of no value for the identification of those at risk of sudden death or recurrent myocardial infarction. Several previous reports suggested that the incorporation of the additional information obtained from analysis of changes in R-wave amplitude increases the sensitivity and specific-

ity of exercise testing, especially in patients with coronary artery disease in whom nonspecific baseline abnormalities make it more difficult to interpret ST-segment changes.[7-10] However, other studies suggested that analysis of R-wave changes does not provide any useful additional information.[11-13]

Exercise testing is frequently used in patients who have had a recent myocardial infarction and has been demonstrated to provide useful prognostic information.[14-16] Two studies that reported on the prognostic value of changes in R-wave amplitude during exercise testing after myocardial infarction produced conflicting results. Poyatos et al[4] studied the predictive value of exercise-related changes in R-wave amplitude in 146 patients with angiographically documented coronary heart disease who were followed for 6 years. They showed that in a subset of 96 patients with previous myocardial infarction, the incidence of coronary events (myocardial infarction or cardiac death) was 48.8% in those with an increased R-wave amplitude compared with 27.3% in those with a decreased R-wave amplitude.

Hsu et al,[3] using a discriminant analysis, showed that in patients with recent myocardial infarction, a decreased R-wave amplitude during submaximal exercise testing was associated with an increased risk of subsequent cardiac events. The discordant results of these studies may reflect differences in the populations studied; patients studied by Hsu et al[3] had recent infarcts, whereas in the study by Poyatos et al[4] there is no information regarding the date of the infarct.

In the present study, all patients underwent exercise testing within 2 months of a first acute myocardial infarction. Our results suggest that changes in R-wave amplitude during exercise are not of value in the prediction of recurrent myocardial infarction or subsequent cardiac death in this group of patients. Wolthuis et al[6] suggested that all subjects have a similar R-wave response with an increase in amplitude up to a heart rate of 130 beats/min and a decrease only above this level. They suggested that the "abnormal" response in patients with coronary disease can be explained on the basis of the lower heart rate achieved by this group. The fact that most patients who achieved a heart rate >130 beats/min in the present study had an increased R-wave amplitude suggests that this is not the case. However, whether we considered all patients or only those who achieved heart rates >130 beats/min, the results of the discriminant analysis were the same.

In the present study (as in several previous reports), maximal heart rate achieved during exercise was the variable most strongly associated with subsequent cardiac death; exercise-induced supraventricular arrhythmias and extent of coronary disease had a weaker predictive value.[1,2,14] No exercise test variables had a predictive value for recurrent myocardial infarction. This finding (which confirms the results of previous studies)[16,17] is consistent with the fact that although atherosclerotic coronary disease is common, ischemic events are unpredictable and not necessarily related to the severity or extent of underlying disease.

R-wave amplitude changes were significantly correlated with the presence of angina during follow-up. This may reflect the correlation of increased R-wave amplitude with the severity of ischemia detected by exercise testing and the extent of underlying coronary disease. Although the mechanism of changes in R-wave amplitude remains controversial, a link between exercise-related R-wave changes and severity of coronary heart disease was suggested by the study of Baron et al,[10] which showed that the greatest changes in R-wave voltage occurred in patients with either 3-vessel or left main stem disease.

Study limitations: This study was retrospective, but included a relatively large number of patients; in the present era of more aggressive management of myocardial infarction it would be difficult to design an appropriate prospective study. At the time of this study, thrombolytic therapy was infrequently used in our institution, and thus the results may not apply to such patients.

Implications: An increased R-wave amplitude during exercise after a first myocardial infarction was associated with the presence of angina at follow-up, but had no predictive value for the occurrence of cardiac death or recurrent infarction. This association with subsequent angina appears to be related to the presence of more severe underlying coronary disease.

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Effects of Captopril on Left Ventricular Systolic and Diastolic Function After Acute Myocardial Infarction

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The left ventricle progressively dilates in some patients after acute myocardial infarction (AMI). Both systolic and diastolic left ventricular (LV) dysfunction can be of significance in the development of heart failure. Captopril has been shown to prevent dilatation, but the effect on LV diastolic function is unknown. In a placebo-controlled double-blind parallel study, 58 AMI patients with heart failure or low ejection fraction, or both, were consecutively randomized at day 7 to either placebo or captopril (25 mg twice daily). No differences were present between the groups at baseline. Fifty-three patients completed the 6-month study period. Both LV diastolic and systolic volume indexes increased significantly in the placebo group (17 and 14%, respectively); in the captopril group there was no change in LV diastolic volume index, but a 13% reduction in LV systolic volume index. Ejection fraction increased significantly in the captopril group. The peak flow velocities of the early and atrial filling phases were measured, and the ratio between the velocities was calculated. A significant reduction was observed during the study period in early peak flow velocity (65 to 52 cm/s) and in the ratio between early and atrial peak flow velocity (1.3 to 0.8) in the placebo group (p <0.05), but no significant changes occurred in the captopril group. No correlation was found between dilatation of the left ventricle and reduction in early peak flow velocity or the ratio between early and atrial peak flow velocity. In conclusion, captopril prevented LV dilatation, improved ejection fraction and prevented LV diastolic dysfunction in AMI patients with early signs of LV systolic dysfunction.

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Progressive systolic and diastolic left ventricular (LV) dilatation has been observed during the first year after acute myocardial infarction (AMI).[1,2] Captopril can prevent LV dilatation in patients presenting with LV systolic dysfunction in the first few weeks after AMI; furthermore, it probably improves systolic function, as reflected by the ejection fraction.[2,3] This has also been shown in a group of unselected patients with a Q-wave AMI.[4] LV diastolic function after AMI has not been studied to any great extent, even though approximately one third of all patients developing heart failure have abnormal diastolic function, despite the fact that systolic function is normal.[5] One of the most frequently used methods of evaluating LV diastolic function is to measure the transmitral flow by means of Doppler echocardiography.[6] Transmitral flow can be divided into the early and late atrial filling phases, the latter resulting from atrial contraction. The magnitude of the early filling phase and the ratio between the early and atrial phase, both in terms of volume and velocity, depend on the pressure gradient across the mitral valve.[7] The early peak flow velocity and the ratio between early and atrial peak flow velocity are increased when high pressure is present in the left atrium (i.e., in cases of severe heart failure)[8] and decreased when LV wall compliance is reduced (i.e., coronary artery disease,[9] arterial hypertension[10] and hypertrophic cardiomyopathy[11]). Because captopril can prevent LV dilatation, it is probable that it would also be beneficial regarding systolic (expressed as ejection fraction) and diastolic (expressed as early peak flow velocity and the ratio between early and atrial peak flow velocity) function.

METHODS

Patient selection: Patients aged ≤70 years with AMI were included in the study provided they fulfilled at least 1 of the following 2 criteria: signs of heart failure needing diuretics within 5 days of the onset of AMI, and LV ejection fraction ≤45%, as determined by echocardiography on day 5 after AMI. Patients were excluded if they were receiving medication for heart failure before admission (digitalis, angiotensin-converting enzyme inhibitors, diuretics or vasodilatators), or had systolic blood pressure <100 mm Hg, atrial fibrillation, valvular heart disease, LV aneurysm, serious systemic disease, hepatic or renal impairment (serum creatinine >150 μmol/liter), or ejection fraction <25%.

Patient cohort: There were 58 consecutive patients complying with the criteria who could be randomized

TABLE I Demographic Variables of Patients with Acute Myocardial Infarction

Characteristics	Captopril (n = 30)	Placebo (n = 28)
Age (yr)	60 (35–70)	58 (44–70)
Women/men	4/26	2/26
Height (cm)	175 (160–190)	176 (159–195)
Weight (kg)	76 (59–94)	83 (60–105)
Previous AMI	2	1
Systemic hypertension	5	5
Diabetes mellitus	4	4
Anterior/inferior infarct	16/14	15/13
Q-wave/non-Q-wave infarct	21/9	20/8
Peak creatine kinase B (U/L)	81 (17–216)	77 (24–276)
Killip classification (1/2/3)	12/15/3	13/15/0
Treated with streptokinase	24	23

Values are mean (range). Between-group comparisons are not significant. AMI = acute myocardial infarction.

TABLE II Baseline Echocardiographic Measurements of Left Ventricular Volumes and Transmitral Peak Flow Velocities

Parameters	Captopril (n = 30)	Placebo (n = 28)
LV end-diastolic volume index (ml/m^2)	71 (3)	71 (4)
LV end-systolic volume index (ml/m^2)	44 (3)	43 (3)
Stroke volume index (ml/m^2)	28 (1)	28 (1)
Ejection fraction (%)	39 (1)	40 (1)
Early peak flow velocity (cm/s)	65 (3)	66 (3)
Atrial peak flow velocity (cm/s)	56 (3)	56 (3)
Ratio between early and atrial peak flow velocity	1.3 (0)	1.3 (0)

Values are mean (SE). Between-group comparisons are not significant. LV = left ventricular.

during the study period (September 15, 1989 to June 16, 1990). Thirty patients were randomized to the captopril group and 28 to the placebo group.

Study design: Patients were randomized on day 7 after AMI to receive either captopril or placebo in a double-blind parallel trial. A test dose of 6.25 mg of captopril or placebo was blindly administered; this was followed by either placebo or captopril (12.5 mg twice daily) for the next 14 days. The dosage was doubled to 25 mg twice daily provided a clinical examination indicated that this was permissible. Thereafter the medication was continued for the remainder of the trial period (i.e., 6 months). Patients were reviewed both clinically and by echocardiography on days 30, 90 and 180 after inclusion. All patients were administered medication for heart failure (furosemide) and post-AMI medicine (acetylsalicylic acid, β blockers, calcium antagonists or long-acting nitrates, or a combination) if necessary, according to the standard treatment of the department.

Measurements: Echocardiography was performed according to a standardized procedure by 2 investigators (COG, PS). Patients were examined lying in the left lateral position. The echocardiographic recordings were obtained during normal respiration at the end of the expiration phase. Measurements were obtained on the screen of the echocardiograph, and hard copies were taken for documentation. Volumes were measured using the single-plane area-length method in the apical 4-chamber view.[12] The mean of 3 measurements was used. LV end-systolic, end-diastolic and stroke volume indexes were calculated and corrected for body surface area, and ejection fraction was determined. Transmitral flow was obtained from the apical 4-chamber view between the mitral leaflets by using pulsed-wave Doppler echocardiography (transducer: 2 mHz; and sample length: 2 mm). Early and atrial peak flow velocities were measured, and the ratio between early and atrial peak flow velocity was calculated. A mean of 5 measurements was used.

Statistical analysis: Baseline characteristics were compared using the chi-square test for categoric vari-

ables and the unpaired t test for continous variables. Treatment effects were tested using the Wilcoxon signed-rank test for paired data in relation to ingroup parameters and the Mann-Whitney rank test for unpaired data in relation to between-group parameters. A p value <0.05 was considered statistically significant. Comparison between the changes in LV volumes and transmitral peak flow velocities were examined using correlation analysis.

RESULTS

Baseline evaluation: At baseline the 2 treatment groups had similar clinical characteristics (Table I) and echocardiographic measurements (Table II).

Patient withdrawals: In the captopril group, 1 patient died, 1 was lost to follow-up and 1 underwent coronary bypass surgery. In the placebo group, 1 patient had reinfarction on the day before the 6-month follow-up examination, and 1 had 2 reinfarctions and subsequently underwent coronary bypass surgery. Thus, 53 patients completed the study (27 in the captopril group and 26 in the placebo group).

Additional medication: Of the 53 patients completing the study, at inclusion 11 in the captopril group and 9 in the placebo group received furosemide. At completion of the trial, 3 patients in the captopril group and 8 in the placebo group received furosemide. No other diuretics were used.

During the study period, 49 patients were administered antiischemic medication (25 in the captopril group and 24 in the placebo group). Nineteen patients in both groups were administered β blockers.

Left ventricular volumes: Both LV end-diastolic and end-systolic volume indexes increased significantly (71 to 83 ml/m^2 [+17%], and 43 to 49 ml/m^2 [+14%], respectively) during the study period in the placebo group. In contrast, the captopril group had no change in LV end-diastolic volume index and a significant reduction in LV end-systolic volume index (45 to 39 ml/m^2 [−13%]). Stroke volume index increased significantly in both groups; ejection fraction had a slight but insignificant increase (40 to 41%) in the placebo group, whereas there was a highly significant increase in the captopril group (39 to 48%). The changes occurred gradually

during the course of the study period, and the difference between the groups was significant concerning LV end-systolic volume index and ejection fraction from 90 days and after (Figure 1).

Transmitral flow: Early peak flow velocity decreased significantly during the study in the placebo group (65 to 52 cm/s), whereas atrial peak flow velocity increased (55 to 67 cm/s), resulting in a significant decreased in the ratio between early and atrial peak flow velocity (1.3 to 0.8). No significant changes were observed in the captopril group, but there was a slight, insignificant increase in the ratio between early and atrial peak flow velocity (1.2 to 1.3); this may be attributed to a reduction in atrial peak flow velocity. These changes devel-
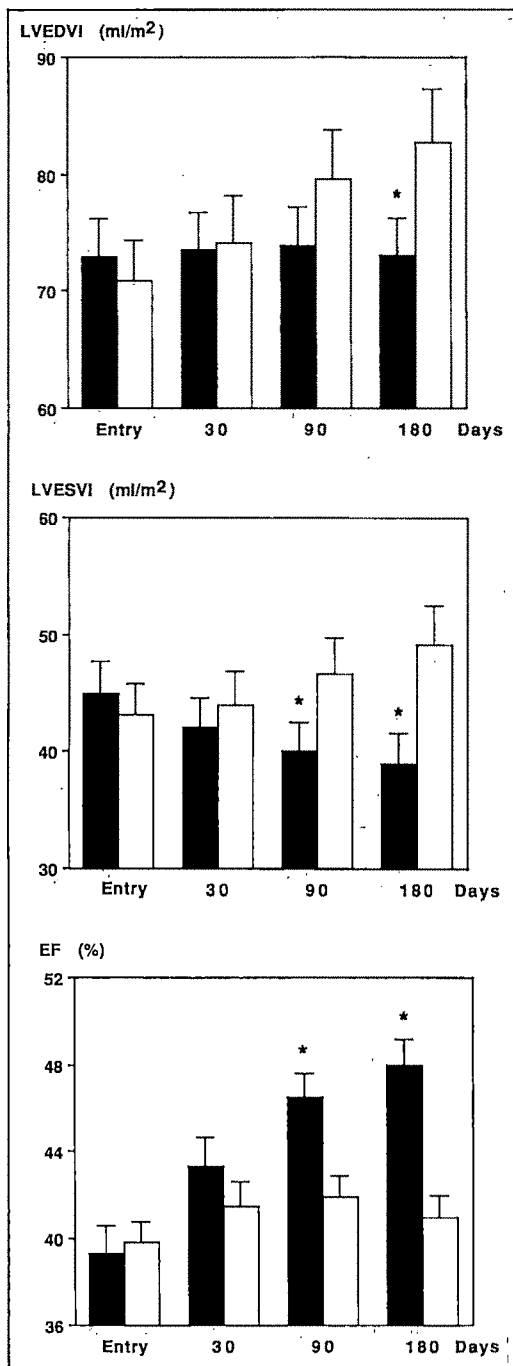
FIGURE 1. Left ventricular volumes and ejection fraction (EF) during 6-month period after acute myocardial infarction. Differences between captopril (*black columns,* n = 27) and placebo (*white columns,* n = 26). Comparisons are between groups. LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; *p <0.05.
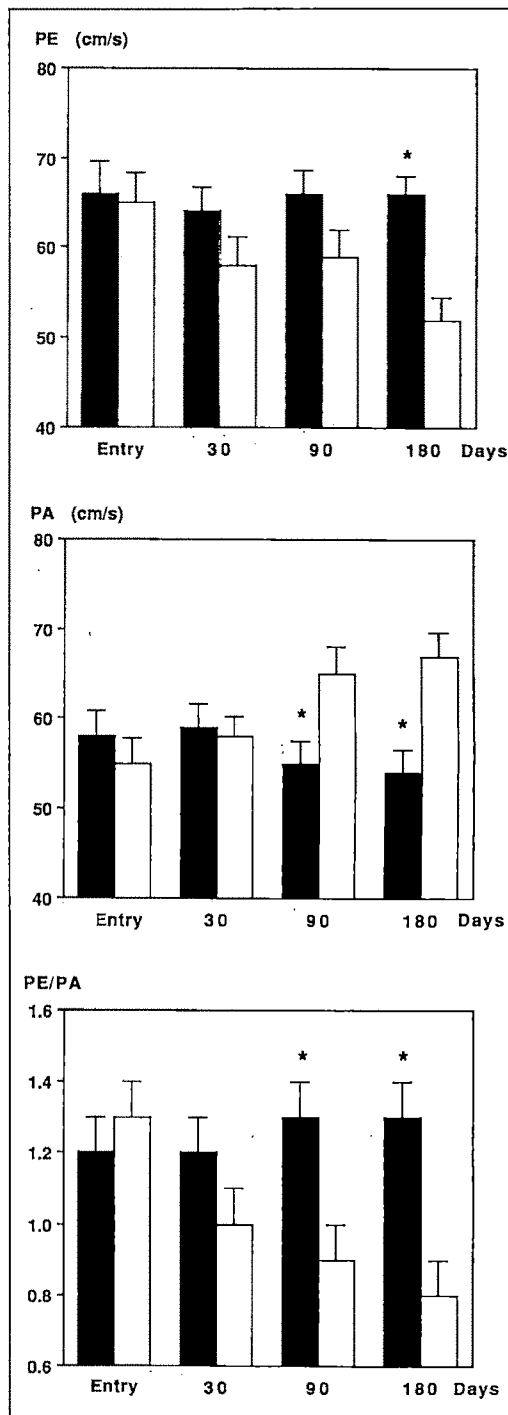
FIGURE 2. Transmitral peak flow velocities during 6-month period after acute myocardial infarction. Differences between captopril (*black columns,* n = 27) and placebo (*white columns,* n = 26). Comparisons are between groups. PA = atrial peak flow velocity; PE = early peak flow velocity; *p <0.05.

oped gradually during the study, and the differences be-
tween the 2 groups were significant at 180 days regard-
ing early and atrial peak flow velocities, as well as the
ratio between early and atrial peak flow velocity (Fig-
ure 2).

Analysis of the correlation between the changes in
LV volume and transmitral flow showed low correlation
coefficients, with no r values >0.29, neither for analysis
of changes in the total group nor for the 2 treatment
groups separately.

Heart rate and mean arterial blood pressure: There
was no difference between the groups regarding either
heart rate or mean arterial blood pressure at inclusion,
and no significant changes occurred in the heart rate of
either group. Mean arterial blood pressure increased
significantly in the placebo group (90 to 99 mm Hg),
whereas there was a slight but insignificant decrease in
the captopril group (92 to 90 mm Hg) (Table III).

DISCUSSION

When AMI involves larger areas of the left ventri-
cle, stretching and remodeling occurs in the parts unaf-
fected by the infarction; the net result is overall dilata-
tion of the ventricle. The short-term hemodynamic ben-
efit is restoration or improvement of stroke volume as a
result of the Starling mechanism.[3,13] However, in the
long-term, LV dilatation after AMI is probably the
forerunner to development of manifest congestive heart
failure and a predictor of poor survival.[14,15]

Presuming that signs of heart failure and low ejec-
tion fraction in the first few days after AMI are mark-
ers of a more widespread infarction, we selected and
consecutively randomized patients that can be regarded
as at high risk for progressive LV dilatation.

The method used in the present investigation for
measuring LV volume is standardized. It can be per-
formed as serial measurements in the same patient. The
method has a high reproducibility and accuracy, al-
though a systematic undermeasurement of absolute vol-
ume occurs.[12]

Similar to Sharpe et al,[2,4] we found a significant in-
crease in both diastolic and systolic volume in the place-
bo group, whereas patients treated with captopril had
no increase in diastolic volume and a significant reduc-
tion in systolic volume. We also, found a significant im-
provement of LV ejection fraction in the captopril
group compared with that of the placebo group.

When primary reduction in myocardial compliance
is present (i.e., with hypertension and amyloidosis), the
diastolic function in itself may be an important stage in
the development of heart failure.[5,16]

There is no single method that may be used to char-
acterize LV diastolic function, but Doppler echocardi-
ography is a widely used tool in the clinical situation.
With regard to the parameters obtained by this method,
early and atrial peak flow velocities can be measured
with high accuracy, and early peak flow velocity and
the ratio between early and atrial peak flow velocity
have a positive correlation to LV end-diastolic pressure
as measured by catheterization.[8]

TABLE III Heart Rate and Mean Arterial Blood Pressure
(captopril [n = 27] and placebo [n = 26])

		Days After Randomization		
	Entry	30	90	180
Heart rate				
Captopril	64 (1)	65 (1)	66 (1)	65 (1)
Placebo	65 (1)	66 (1)	67 (1)	67 (1)
Mean arterial BP				
Captopril	92 (2)	91 (1)	90 (1)	90 (1)
Placebo	90 (2)	93 (2)*	98 (2)*†	99 (2)*†

*p <0.05 compared with at entry; †p <0.05 compared between groups.
Values are mean (SE).
BP = blood pressure.

Transmitral flow changed in the placebo group be-
tween early (passive) and atrial filling; this resulted in a
significant decrease in the ratio between early and atrial
peak flow velocity. In the captopril group, early peak
flow velocity remained constant, whereas atrial peak
flow velocity decreased slightly. These changes occurred
gradually during the entire observation period. The ra-
tio between early and atrial peak flow velocity in the
placebo group 180 days after AMI was within the limits
of measurements obtained in patients with coronary ar-
tery disease,[8] whereas the values in the captopril group
were identical to those of normal subjects of the same
age.[17]

An increase in preload tends to increase early peak
flow velocity, but the lower need for diuretics in the cap-
topril than in the placebo group indicates that this does
not apply in our study; furthermore, a reduction in pul-
monary capillary wedge pressure, as demonstrated by
Pfeffer et al[3] in patients treated with captopril, also ex-
cludes this possibility. There was no difference between
the 2 groups with regard to antiischemic medication,
and no change in heart rate. Mean arterial pressure in-
creased significantly in the placebo group, but remained
constant in the captopril group throughout the trial pe-
riod. The long-term effect of a reduction in arterial
pressure on the transmitral flow is not known, but there
is little effect of an acute reduction.[18]

The most obvious explanation for the changes in
transmitral flow in the placebo group is a reduction in
the compliance of the LV wall. Dilatation in itself de-
creases the distensibility of the LV wall.[7] However, the
absence of correlation observed between changes in LV
volumes and transmitral flow implies that other factors
are involved. Because captopril has shown a positive ef-
fect on coronary blood flow in animal experiments,[19]
prevention of ischemia and secondary fibrosis may in-
fluence the compliance and transmitral flow.

Although protection against LV dilatation and isch-
emia may be involved in the beneficial effect on diastol-
ic function, these observations may be directly influ-
enced by some other underlying mechanisms. The effect
of captopril on the local cardiac renin angiotensin sys-
tem, bradykinin and prostacyclin, as well as the scav-
enging of toxic-free oxygen radicals is poorly elucidated
at present.[20] Different angiotensin-converting enzyme

inhibitors may produce their effects by different mechanisms.[21]

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Acute and Long-Term Outcome of Narrowed Saphenous Venous Grafts Treated by Endoluminal Stenting and Directional Atherectomy

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Angioplasty of the narrowed saphenous vein by-pass grafts remains a difficult challenge. Over a 37-month period at this institution, 119 of 176 interventions (68%) on saphenous vein grafts (average age 8.3 years from bypass surgery to graft intervention) were performed using either directional coronary atherectomy (n = 35) or Palmaz-Schatz intracoronary stents (n = 84), representing 37% of all stents and 15% of all atherectomies during the study period, respectively. Of the 57 saphenous vein graft lesions treated with conventional balloon angioplasty during this period, 49 (86%) had 1 or more contraindications to stenting or directional atherectomy (thrombus, total occlusion, reference vessel <3 mm in diameter).

The acute success rate was 99% for stents (1 failure to dilate) and 94% for directional atherectomy (2 failures to cross the lesion with the atherectomy device). Lumen diameter increased from 0.9 to 3.6 mm (reference vessel 3.6) for stents, and from 0.9 to 3.5 mm (reference 3.8) for atherectomy (for all comparisons, p = not significant), with no major complications (abrupt or subabrupt closure, emergent coronary bypass surgery, death, or Q-wave myocardial infarctions). During the same time period 50 of 57 vein grafts (88%) rejected for stenting or atherectomy were dilated successfully by conventional balloon angioplasty, with 3 patients (5%) requiring emergent coronary bypass surgery. Angiographic follow-up was available for 50 of 64 eligible patients (78%). Restenosis (defined as ≥50% stenosis at 6-month angiographic follow-up) was present in 13 of 50 lesions (26%, [95% confidence interval: 14%, 38%]), including 8 of 32 stented lesions (25%) and 5 of 18 atherectomy lesions (28%) (p = not significant). These data suggest that saphenous vein bypass

graft stenoses may be treated safely and effectively using Palmaz-Schatz stenting or directional atherectomy, with short- and long-term results that may be better than those traditionally expected with conventional balloon angioplasty.
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Conventional balloon angioplasty of saphenous vein bypass grafts remains a major challenge in coronary angioplasty. Younger grafts (those <3 years old) have a good acute success rate, but the 40 to 70% incidence of subsequent restenosis remains a major clinical problem.[1-9] Older grafts (those >3 years) tend to have more diffuse and friable plaques that are prone to distal embolization and increased cardiac complications when dilated.[4,10] Because repeat bypass surgery carries a significantly higher morbidity and mortality rate than primary surgery,[11] the use of balloon angioplasty in patients who have undergone prior coronary revascularization is still preferred over repeat bypass grafting when the important narrowings are technically approachable. Recently, several new technologies for coronary intervention have been introduced in the interest of improving acute success and safety, or decreasing the subsequent restenosis rate of coronary artery bypass lesions. Based on a 3-year experience with 2 such technologies (directional coronary atherectomy and balloon expandable stents) we have examined their performance in the treatment of saphenous vein graft lesions.

METHODS

Patient population: Between June 1988 and July 1991, 119 of 179 significant narrowings (68%) in saphenous vein bypass grafts were treated using either a Palmaz-Schatz intracoronary stent (Johnson and Johnson Interventional Systems, Warren, New Jersey, n = 84) or directional coronary atherectomy (Devices for Vascular Intervention, Inc. Redwood City, California, n = 35). Although these patients accounted for only 8% of the total coronary interventions performed during the study period, they accounted for 34% of all stents and 16% of all atherectomies.

Interventional procedures and angiographic measurements: Intracoronary stenting was performed using a single 15 mm articulated Palmaz-Schatz stent, described previously[12] (Figures 1 and 2). Intensive antico-

agulation included heparin, dextran, aspirin and dipyridamole and was initiated before stent placement, whereas aspirin and dipyridamole were continued indefinitely, and wafarin for 3 months, after discharge. Directional coronary atherectomy was performed using either a Simpson Coronary Atherocath as described previously[13] (Figures 3 and 4).

All patients were requested to have follow-up angiography at 6 months after intervention. Patients who underwent earlier (<4 months) restudy for the evaluation of recurrent symptoms, but were found to have ≤70% diameter stenosis, were accepted for analysis only if they returned for repeat angiography ≥6 months after the procedure. Both the acute (pre- and postprocedure) and the 6-month (follow-up) angiograms were analyzed. The minimal luminal diameter of each treated lesion was measured from optically magnified images compared with the known diameter of the angiographic
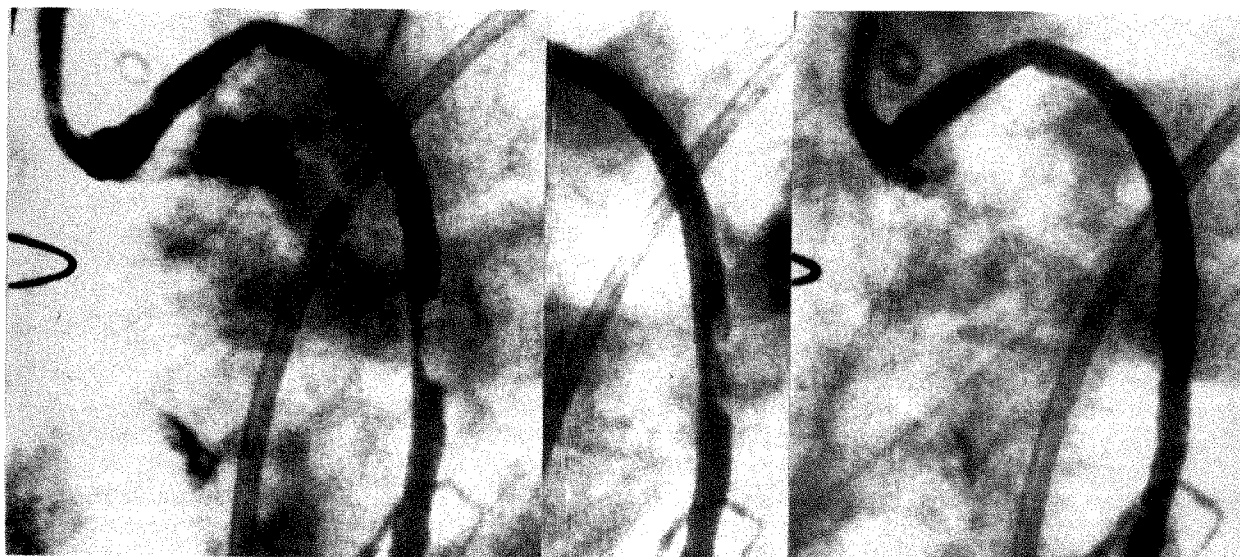
FIGURE 1. Vein graft stent. *Left panel,* eccentric stenosis in midportion of saphenous vein graft. *Middle panel,* results after conventional balloon angioplasty shows a severe and disrupted residual stenosis. *Right panel,* final result after placement of a single endoluminal stent.
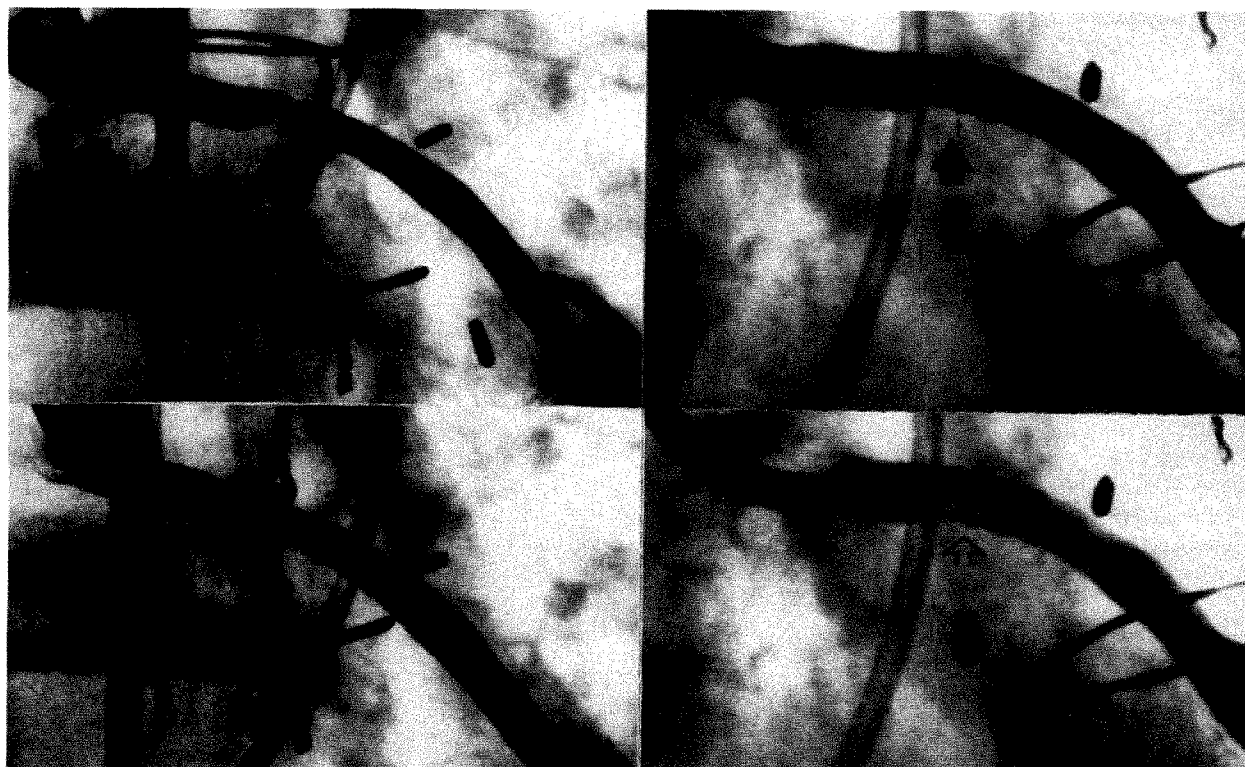
FIGURE 2. Vein graft stent. *Top left panel,* eccentric stenosis in the proximal portion of saphenous vein graft. *Bottom left panel,* 50% residual narrowing after conventional percutaneous transluminal coronary angioplasty. *Top right panel,* results after placement of a single intracoronary stent. *Bottom right panel,* washout cineangiographic frame shows the strut pattern of the expanded stent within the area of the prior stenosis.

catheter.[14,15] The reference size was the mean of the diameter of the reference segment proximal and distal to the treated lesion. Based on these measurements, 2 important parameters were derived: acute gain was defined as the increase in the absolute diameter of the treated segment immediately after the procedure, whereas the late loss was defined as the decrease in absolute diameter of the treated segment from the post-
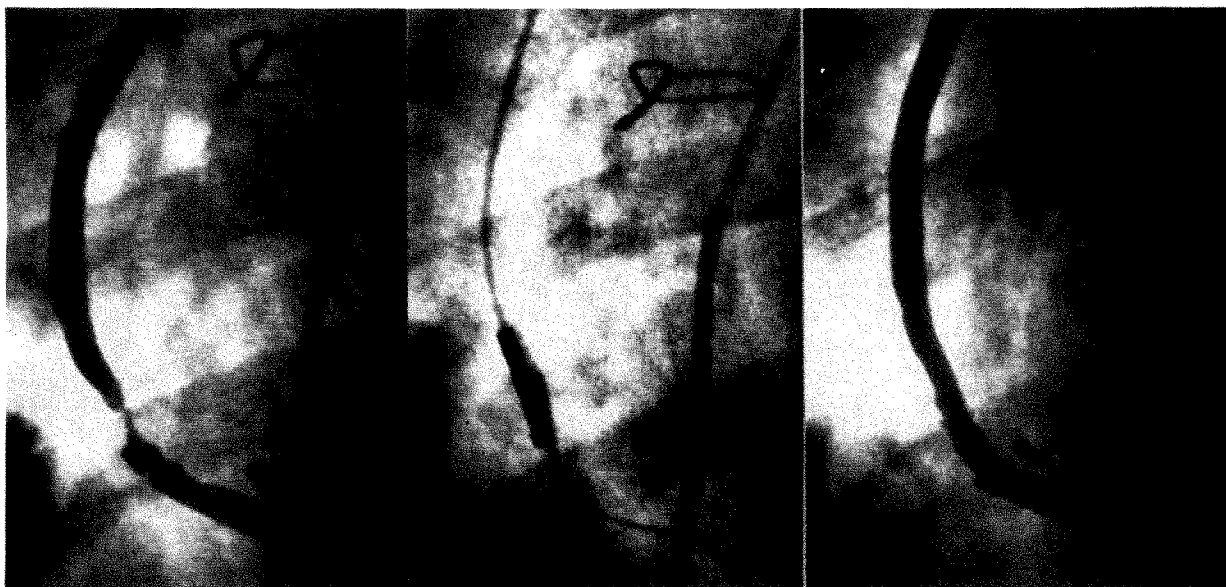
FIGURE 3. Vein graft atherectomy. *Left panel,* eccentric stenosis in distal portion of saphenous vein graft. *Middle panel,* directional atherectomy device positioned across the stenosis, with the balloon inflated toward right and cutter housing facing the left side of the photo. *Right panel,* results after multiple circumferential atherectomy cuts.
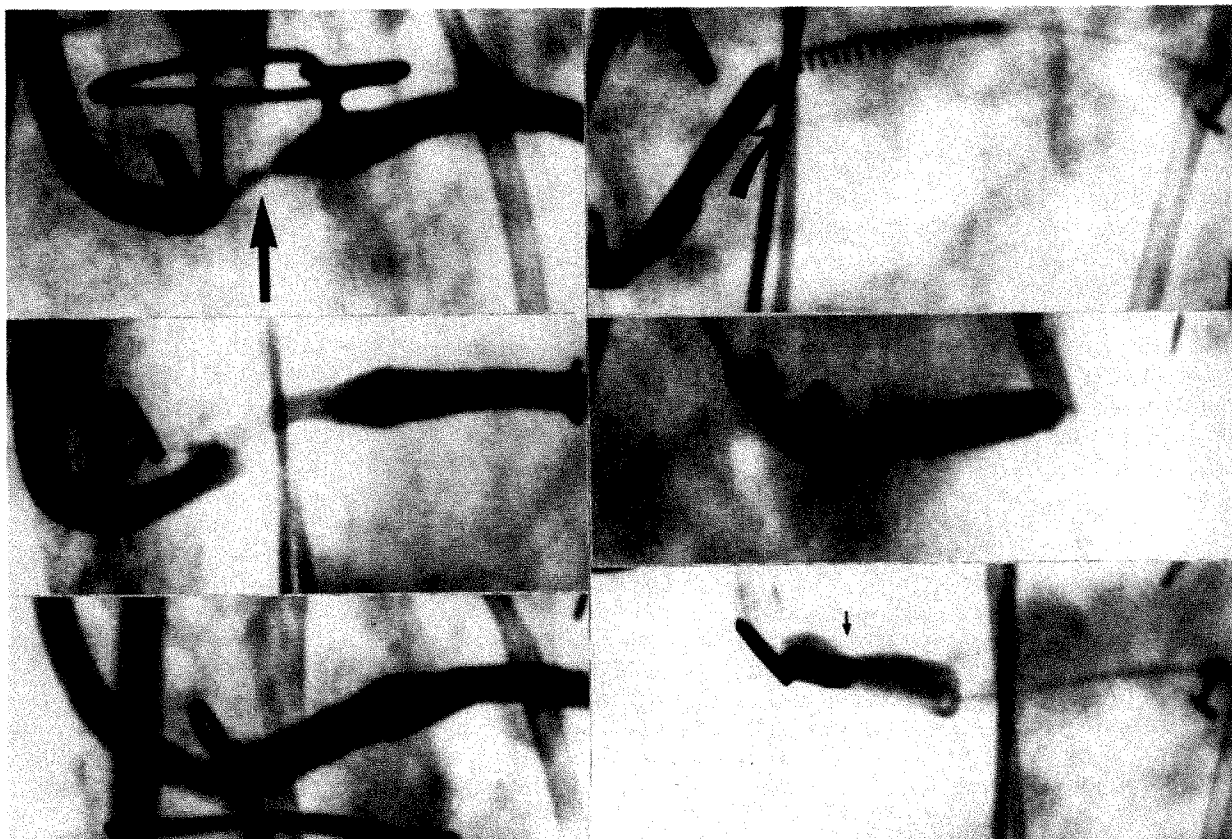
FIGURE 4. Ostial vein graft atherectomy. *Top left panel,* tight ostial stenosis in saphenous vein graft. *Top right panel,* a 7Fr atherectomy device was initially unable to cross the stenosis. *Middle right panel,* dilatation was then carried out with a conventional angioplasty balloon to facilitate passage of the atherectomy device. *Mid-left panel,* after conventional balloon dilatation a significant residual stenosis remained, but *(bottom right panel)* the atherectomy device was then able to cross the lesion. *Bottom left panel,* results after multiple circumferential cuts with a 7Fr directional atherectomy device.

TABLE I Characteristics in 97 Patients with Saphenous Vein Graft Stenoses Treated with Palmaz-Schatz Stents or Directional Atherectomy

	Stent	Atherectomy	p Value
Patients (n = 97)	69	28	
Segments treated	84	35	
Age	66 ± 10	64 ± 11	NS
Sex (% men)	56 (81%)	26 (93%)	NS
Graft age (years)*	8.5 ± 4	7.6 ± 4.4	NS
Cigarette smoking (%)	35 (51%)	15 (54%)	NS
Diabetes mellitus (%)	18 (26%)	9 (32%)	NS
Systemic hypertension (%)	41 (59%)	13 (46%)	NS
Hypercholesterolemia (%)†	44 (64%)	17 (61%)	NS
Family history of CAD (%)	41 (59%)	14 (50%)	NS
Left ventricular ejection fraction (%)	47 ± 18	56 ± 15	NS

*Calculated from time of bypass surgery to coronary intervention.
†Defined as serum total cholesterol > 200 mg/dl.
CAD = coronary artery disease; NS = not significant.

TABLE II Immediate Results

	Stent	Atherectomy
Lesion success	83/84 (99%)	33/35 (94%)
Characteristics of stenosis		
Ostial (%)	0 (%)	14 (40%)*
Eccentric (%)	34 (40%)	21 (61%)†
Calcified (%)	3 (4%)	3 (8%)
Length (mm)	6.5 ± 3.5	5.2 ± 3.6
Prior restenosis	24/84 (28%)	8/35 (23%)
Measurements before procedure		
Reference (mm)	3.62 ± 0.68	3.80 ± 0.83
Stenosis diameter (mm)	0.90 ± 0.64	0.86 ± 0.60
Percent stenosis (mm)	75 ± 17	78 ± 15
Measurements after procedure		
Stenosis diameter (mm)	3.57 ± 0.61	3.47 ± 58
Percent stenosis (mm)	0 ± 14	5 ± 17
Acute gain (mm)	2.77 ± 0.86	2.67 ± 0.82

*p = 0.001; †p = 0.03.

TABLE III Complications

	Stents	Atherectomy
Major complications	0	0
Q-wave myocardial infarction	0	0
Emergent bypass surgery	0	0
Death	0	0
Other complications		
Vascular	5 (5%)	2 (6%)
Non-Q-wave myocardial infarction	9 (10%)	1 (3%)

time from the onset of acute symptoms to the interventional procedure (55 days, range 0 to 372) and the age of the treated saphenous vein grafts (8.3 years, range 3 months to 20 years, from bypass surgery to graft intervention) was also similar between the 2 groups, whereas 86% of treated grafts were aged >3 years.

Immediate results: Successful stent placement was performed in 83 of 84 segments (99%) (1 failure to dilate) and successful atherectomy was performed on 33 of 35 segments (94%) (2 failures to cross the stenosis with the atherectomy catheter, Table II). New (nonrestenosis) lesions accounted for 72% of stented vessels and 77% of atherectomized vessels. Most lesions were located in the midportion of the treated graft, although 14 ostial lesions were treated with atherectomy. Eccentric lesions were more prevalent in patients with atherectomies (61%) versus those with stent (40%, p = 0.03), but the average reference diameter (3.62 vs 3.80 mm), lumen diameter before treatment (0.90 vs 0.86 mm) and percent stenosis (75 vs 78%) of the atherectomized and stented vein grafts were similar (p = not significant [NS]). The mean lumen diameter increased from 0.90 to 3.57 mm after stenting, and from 0.86 to 3.47 mm (p = NS), corresponding to an acute gain of 2.77 mm for stents and 2.67 mm for atherectomy (p = NS).

There were no major complications (Q-wave myocardial infarctions, procedural deaths, or emergent coronary bypass procedures) after either stenting or atherectomy (Table III). Distal embolization of graft plaque material was evident by distal branch obstruction in 1 patient treated with stenting and in 1 treated with atherectomy; non-Q myocardial infarction occurred in 9 patients (10%) treated with stenting and in 1 (3%) with atherectomy (p = NS). By comparison, during the same period 3 of 57 conventional angioplasty procedures (5%) in saphenous vein bypass grafts required emergent coronary bypass surgery due to an inability to cross acutely occluded grafts in 2 patients, and abrupt closure following inflation of a long (40 mm) stenosis in 1 patient.

In 27 segments treated with atherectomy, atherosclerotic plaque was present in 81%, thrombus in 63% and intima in 44%. Excision of deep wall components was common, with media present in 35% and adventitia in 19%. There was no association between the presence of either media or adventitia, vessel size, and acute result or restenosis. There was, however, an association between the presence of atherosclerosis or thrombus and graft age (p = 0.03): atherosclerosis was present in all grafts aged >7 years, but in only 64% of younger grafts

procedure to the 6-month follow-up angiogram. The long-term net gain produced by an intervention is thus the difference between its acute gain and late loss.[16]

Statistical methods: All values are reported as the actual count or the mean value ± standard deviation. Analysis of categorical data between groups was done using chi-square, and continuous variables were analyzed by *t* test. Survival and event-free survival estimates were performed using Kaplan-Meier estimates.

RESULTS

Clinical characteristics: Balloon expandable stenting was performed on 84 saphenous vein stenoses in 69 patients (81% men, average age 66 years), and directional atherectomy was performed on 35 saphenous vein stenoses in 28 patients (93% men, average age 64 years, Table I). Clinical characteristics were similar among patients who were treated by either stenting or atherectomy (including hypercholesterolemia defined as cholesterol ≥200 mg%, cigarette smoking, systemic hypertension, diabetes mellitus, family history of coronary disease and left ventricular ejection fraction). The mean

(p = 0.03). In contrast, smooth muscle cell hyperplasia was less common (28%) in grafts aged >7 years, compared with younger grafts (72%, p = 0.03).

During this study period, 57 of the 176 saphenous vein bypass grafts (32%) treated with percutaneous techniques underwent conventional balloon angioplasty. The decision to treat with conventional angioplasty rather than stenting or directional atherectomy was based on contraindications to the newer interventions in 49 cases (86%: diameter <3 mm in 13, marked intraluminal thrombus in 20, severe calcification in 1, or total graft occlusion in 16).

Follow-up: Angiographic follow-up was available in 50 of 64 patients (78%) treated with stenting or atherectomy eligible for 6-month follow-up. The mean follow-up time was 181 ± 57 days (25th percentile, 149 days; 50th percentile, 189 days; and 75th percentile, 218 days). The average stenosis diameter (2.77 vs 2.67 mm) and percent stenosis (36 vs 33%) were similar for stents and atherectomy (p = NS), although late loss in lumen diameter tended to be slightly greater for stents (1.53 mm) than for atherectomy (1.20 mm, p = NS). The rate of restenosis, defined as the presence of ≥50% di-

ameter stenosis at 6-month follow-up angiography, was 26% (95% confidence intervals: 14%, 38%), which was similar between the 2 groups (25% for stents and 28% for atherectomy [p = NS]). Clinical follow-up demonstrated 1- and 2-year survival rates of 90 and 87%, and 1- and 2-year freedom from death, myocardial infarction, coronary bypass surgery or repeat coronary angioplasty in 80 and 74% at 1 and 2 years, respectively (Figure 5).

DISCUSSION

Although balloon angioplasty of saphenous vein grafts can be performed with acceptable acute success and complication rates, up to 70% of the dilated vessels develop restenosis within 6 months of the procedure.[1-9] We report here on a single center experience using 2 newer interventional devices (intracoronary stenting and directional atherectomy) instead of conventional balloon angioplasty for the treatment of selected stenotic saphenous vein grafts. Most patients (69%) who presented with bypass graft stenosis during the study period were considered to be candidates for at least 1 of these new technologies. The remaining patients were treated with
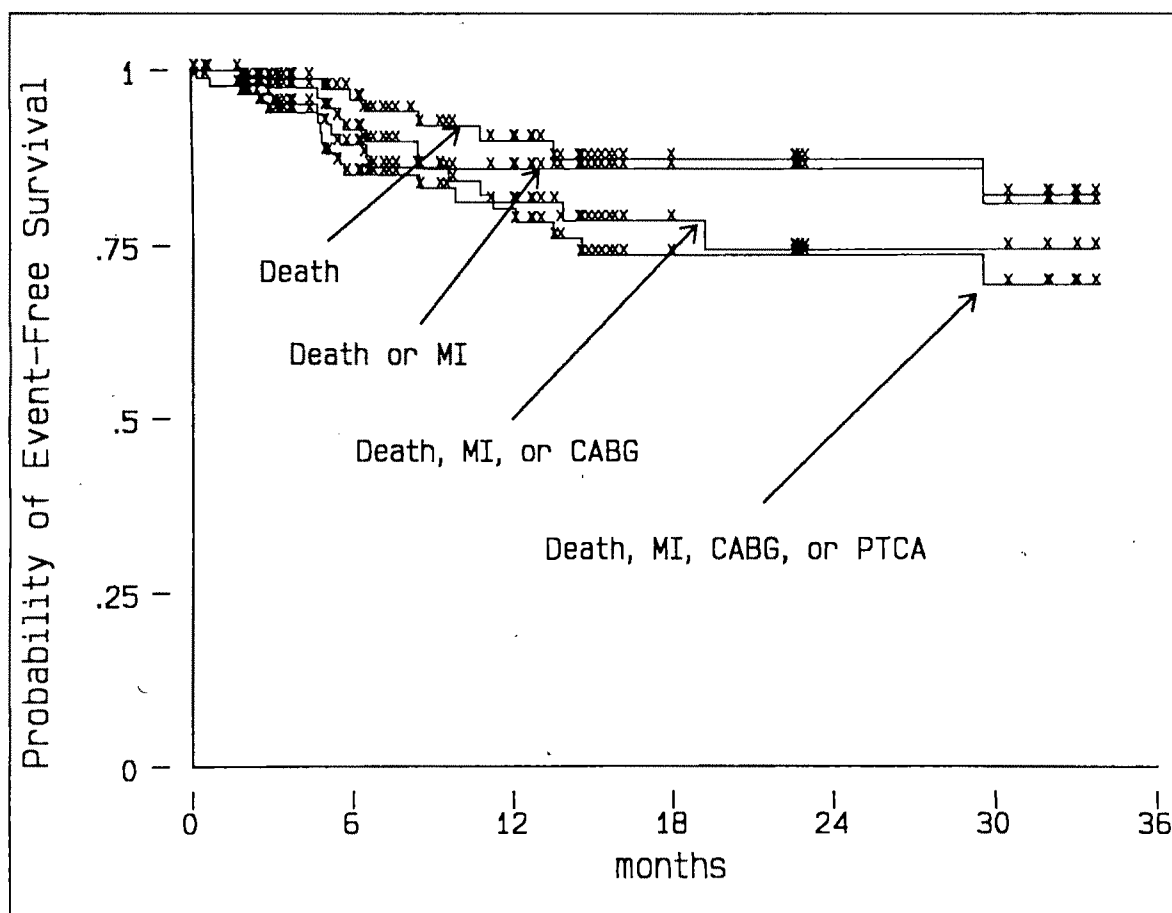
FIGURE 5. Probability of event-free survival after vein graft Palmaz-Schatz stenting or directional atherectomy. The Kaplan-Meier estimates of freedom from: death, death and myocardial infarction (MI); or death, MI and coronary artery bypass grafting (CABG); or death, MI, CABG or conventional percutaneous transluminal coronary angioplasty (PTCA) are shown. The 1- and 2-year probability of freedom from death was 90 and 87%, whereas the 1- and 2-year probability of freedom from death, MI, CABG or PTCA was 80 and 74%.

conventional angioplasty predominantly because they had 1 or more relative contraindications to either stent placement (thrombus, total occlusions) or directional atherectomy (vessel <3 mm, heavily calcified lesion).

Analysis of acute results revealed very high acute success rates (99% success for stenting and 93% success for atherectomy), comparable or superior to those reported for conventional angioplasty of saphenous vein grafts.[1-9] In fact, procedural success and safety were similar to that for atherectomy and stenting in native vessels.[17-21] This is particularly remarkable given the high (86%) fraction of our patients whose saphenous vein grafts were >3 years old.[1-3,7]

Six-month angiographic follow-up was available for 78% of eligible patients, and showed a 26% restenosis rate, significantly lower than that previously reported for conventional angioplasty in similar lesions.[1-9] Moreover, our study population was significantly larger than most previous reports, and the completeness of angiographic follow-up was greater. Thus, the restenosis rate in the current study compares favorably to those previously reported after directional atherectomy in saphenous vein bypass grafts,[22-25] and is similar to the multicenter experience with Palmaz-Schatz stenting in saphenous grafts.[26] These apparently lower restenosis rates may be related to the fact that we have traditionally attempted to obtain the largest, safely possible acute lumen diameters with both stenting and atherectomy, in accord with our observation that larger lumen diameters immediately following the procedure correlate with a lower subsequent restenosis rate.[16,27-30]

The histologic analysis performed on atherectomy specimens reveals an interesting pattern: lesions in older grafts are more likely due to atherosclerosis, whereas lesions in younger grafts (including those at the aortoostial junction) are more likely due to intimal hyperplasia.[31] This extends prior observations on changing histology with graft age based on autopsy data.[32,33]

Study limitations: This study was an observational rather than a prospective, randomized trial, in which patients were selected for a particular treatment at the discretion of the operator, based on lesion characteristics and vessel size. Although the patients we excluded from stent or directional atherectomy had a lower success and a higher complication rate, this may well have been due to their more unfavorable anatomy rather than an inherent superiority of stenting or atherectomy over conventional balloon angioplasty. Similarly, our restenosis rates cannot be evaluated fully without access to a comparable group of patients undergoing conventional balloon angioplasty, but 2 such randomized trials for the treatment of vein graft stenosis, CAVEAT II (balloon angioplasty versus directional atherectomy) and STRESS (balloon angioplasty versus Palmaz-Schatz stenting), are currently in progress. However, we can state that nearly all patients with vein graft lesions who presented without specific technical contraindication to stenting or directional atherectomy were successfully treated with 1 of these technologies, with good short- and long-term outcome.

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Comparison of Accuracy for Detecting Coronary Artery Disease and Side-Effect Profile of Dipyridamole Thallium-201 Myocardial Perfusion Imaging in Women Versus Men

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Intravenous dipyridamole planar thallium-201 imaging is a safe and effective test for detection and prognosis of coronary artery disease (CAD) in the general population. The relative diagnostic accuracy and side-effect profile of dipyridamole thallium-201 stress imaging in women is not defined. Forty-three consecutive female and 71 male patients who underwent dipyridamole thallium-201 imaging (0.56 mg/kg) within 3 months of cardiac catheterization were studied. Scans were considered abnormal if fixed or reversible perfusion defects were detected. Stenosis severity of ≥50% luminal diameter reduction of any artery defined CAD. Overall sensitivity for detection of CAD was 0.87 in women and 0.94 in men; specificity was 0.58 in women and 0.63 in men (p = not significant). Sensitivity for detection of 1-vessel CAD was 0.60 in women and 0.94 in men (p = 0.001). The sensitivity for detection of multivessel CAD (with or without surgical revascularization) was 1.0 and 0.94 in women and men, respectively. Adverse effects were reported in 62% of women and in 38% of men (p = 0.01). There was no significant difference in the incidences of chest pain, headache, nausea, flushing or electrocardiographic changes. The incidences of severe ischemia and dizziness were higher in women. Possible explanations for this difference in adverse effects include gender differences in the volume of distribution of dipyridamole due to varied fat-to-muscle ratios and different subjective nocioceptive sensitivities to the effects of dipyridamole. Overall sensitivity and specificity are comparable between the sexes.

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Coronary artery disease (CAD) is common in postmenopausal women, and represents a noninvasive diagnostic challenge. Exercise electrocardiography is known to have a lesser overall diagnostic accuracy in women than in men presenting with chest pain syndromes. The sensitivity and specificity of exercise thallium testing has been shown to be comparable between the sexes if gender-specific artifacts are taken into account.[1,2] Intravenous dipyridamole is a relatively selective coronary arterial vasodilator. When used in conjunction with thallium-201, it is useful for assessing myocardial perfusion abnormalities distal to flow-limiting coronary artery stenoses.[3-6] This approach is frequently applied to patients with limited exercise tolerance in order to detect CAD and to evaluate short- and long-term prognosis.[7-10] This study extends previous reports[11-13] by investigating the diagnostic value and profile side effect of intravenous dipyridamole thallium-201 imaging in women compared with men.

METHODS

Patient population: Retrospective identification of all patients in the St. Louis University Medical Center computerized data base who had undergone dipyridamole thallium imaging between August 1984 and August 1987 was completed. Patients were included in the current analysis if they had undergone cardiac catheterization within 3 months of their dipyridamole test without intervening revascularization procedures. No attempt was made to match the male and female subjects with regard to clinical or angiographic parameters. Patients with uncontrolled, unstable angina or congestive heart failure and those with severe bronchospastic lung disease are not considered candidates for dipyridamole thallium-201 imaging, and were excluded from the study population. The remaining patients in whom thallium-201 imaging data were reviewed included 43 women and 71 men. Indications for dipyridamole thallium-201 testing are summarized in Table I. Table II describes the clinical characteristics of this patient population. Women tended to have more unstable anginal patterns; other characteristics, including major risk factors and use of medications were comparable between men and women studied.

Dipyridamole infusion and imaging protocol: Dipyridamole infusion and planar thallium-201 myocardial imaging, patient preparation and monitoring were performed as previously reported by our laboratory.[7,12] Aminophylline and nitroglycerin were available for treatment of patient side effects. Immediate and de-

layed thallium-201 images interpreted by 2 independent expert reviewers unaware of the clinical and angiographic data. Reviewers were aware of patient gender in order that soft tissue imaging artifact could be fairly evaluated.[13] Scans were considered as abnormal if either fixed or reversible defects were noted.

TABLE I Indication for Dipyridamole Testing

	Women	Men
Incapable of exercising	5	10
Pre-PTCA	0	3
Post-PTCA	4	3
Post–myocardial infarction	4	5
Evaluation of known CAD	13	34
Evaluation of suspected CAD	15	9
Post–unstable angina	2	5
Study protocol	0	1
Other	0	1
Total	43	71

CAD = coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty.

TABLE II Clinical Characteristics of the Study Population

	Women (n = 43)	Men (n = 71)	p Value
Average age (yrs)	63 ± 10	62 ± 7.4	NS
Average weight (lbs)	174 ± 26	185 ± 22	NS
Risk factors			
History of hypertension	25 (58%)	35 (49%)	NS
History of diabetes mellitus	12 (28%)	15 (21%)	NS
Family history	15 (35%)	18 (25%)	NS
Current smoker	15 (35%)	17 (24%)	NS
Hypercholesterolemia	8 (19%)	9 (13%)	NS
Presentation			
Asymptomatic	10 (23%)	17 (24%)	NS
Nonspecific chest pain	13 (30%)	11 (15%)	p = 0.06
Stable angina	6 (14%)	26 (37%)	p < 0.05
Recent MI	1 (2%)	7 (10%)	NS
Crescendo angina	7 (16%)	2 (3%)	p < 0.05
New onset angina	11 (26%)	6 (8%)	p < 0.05
Medications			
β blocker	9 (21%)	26 (37%)	p = 0.07
Calcium antagonist	21 (49%)	38 (54%)	NS
Nitrates	20 (47%)	37 (52%)	NS

MI = myocardial infarction; NS = not significant.
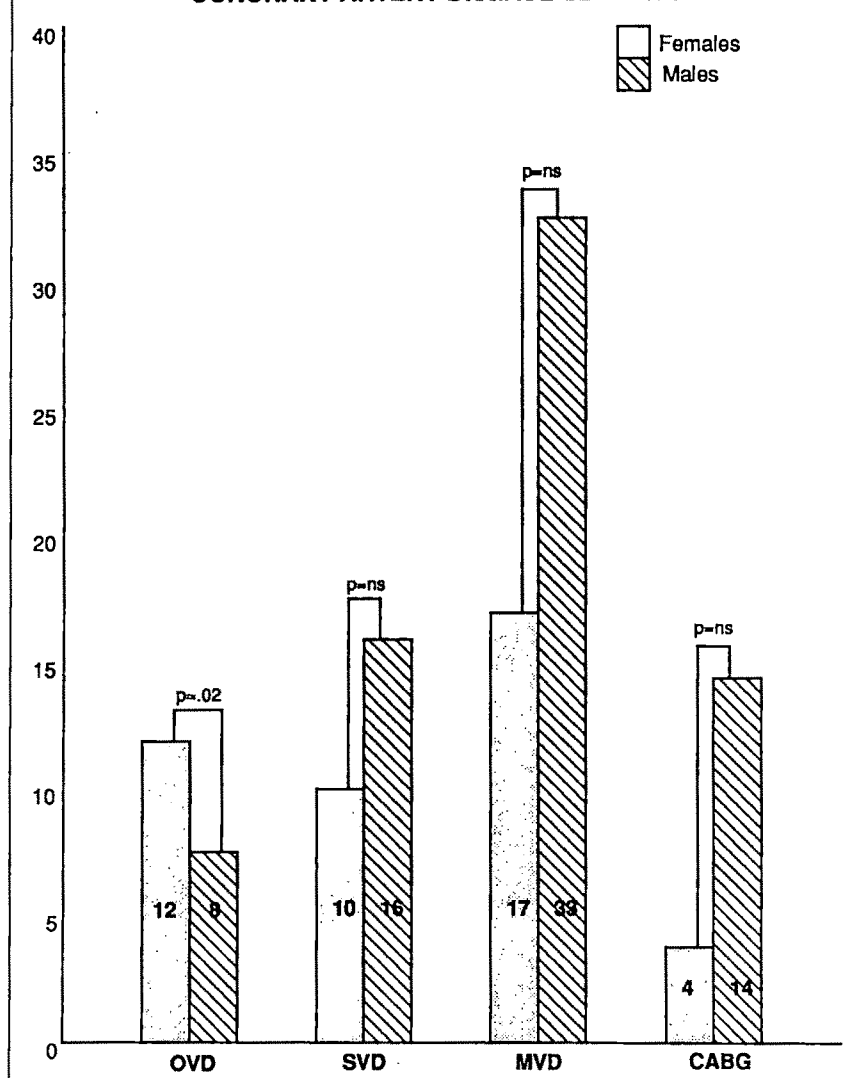
FIGURE 1. Although there was a trend toward more severe coronary artery disease in men, this difference was not statistically significant. CABG = coronary artery bypass graft; MVD = multivessel disease; = not significant; OVD = zero vessel disease; SVD = 1-vessel disease.

CORONARY ARTERY DISEASE SEVERITY

TABLE III	Territory of Coronary Artery Stenosis by Gender			
	LM (%)	LAD (%)	LC (%)	Right (%)
Women	0 (0)	24 (39)	16 (27)	21 (34)
Men	7 (5)	51 (35)	38 (18)	48 (33)
p Value	0.04	NS	NS	0.06

LAD = left anterior descending artery; LC = left circumflex artery; LM = left main artery; NS = not significant; Right = right coronary artery.

Coronary angiography: Selective right and left coronary angiography was obtained within 3 months of the dipyridamole thallium-201 study. A percutaneous approach was used with angiograms obtained in multiple projections. A luminal diameter stenosis >50% was considered significant for subsequent analyses.

Statistical analysis: Each patient was questioned during and after the dipyridamole infusion about the presence of adverse effects, which were not scored as mutually exclusive. Event frequencies were compared using a chi-square analysis. A p value <0.05 was considered statistically significant. For repeat analyses of variables, overall type I error rate was minimized by considering a p value <0.01 as statistically different. The number of narrowed arteries, the prevalence of adverse effects, and aminophylline and nitroglycerin usage were compared between the sexes by chi-square analysis.

RESULTS

Coronary artery disease severity: The distribution of CAD in men and in women is summarized in Table III, with the extent of disease further delineated in Figure 1. There was no difference between the sexes with regard to the severity of CAD, although there was a trend toward female predominance in the subset without significant CAD. An insignificant trend existed in favor of more severe CAD and coronary artery bypass grafting in men. There was no significant difference in the distribution of thallium-201 defects (fixed, 13 vs 5%; reversible, 74 vs 72%; p = not significant [NS]) between men and women.

Sensitivity and specificity: The sensitivity for detection of CAD in women was 0.87 (27 of 31) a value not significantly different from that in men (0.94 or 59 of 63) (Figure 2). Specificity of the dipyridamole thallium-201 scan was 0.58 (7 of 12) in women and 0.63 (5 of 8) in men. Figure 3 depicts the sensitivity of dipyridamole thallium-201 imaging with respect to the extent of CAD. There was a lower sensitivity (0.60 or 6 of 10) for the detection of 1-vessel CAD in women compared with men (0.94 or 15 of 16) (p = 0.01). There was no signifi-

DIAGNOSTIC ACCURACY BY GENDER
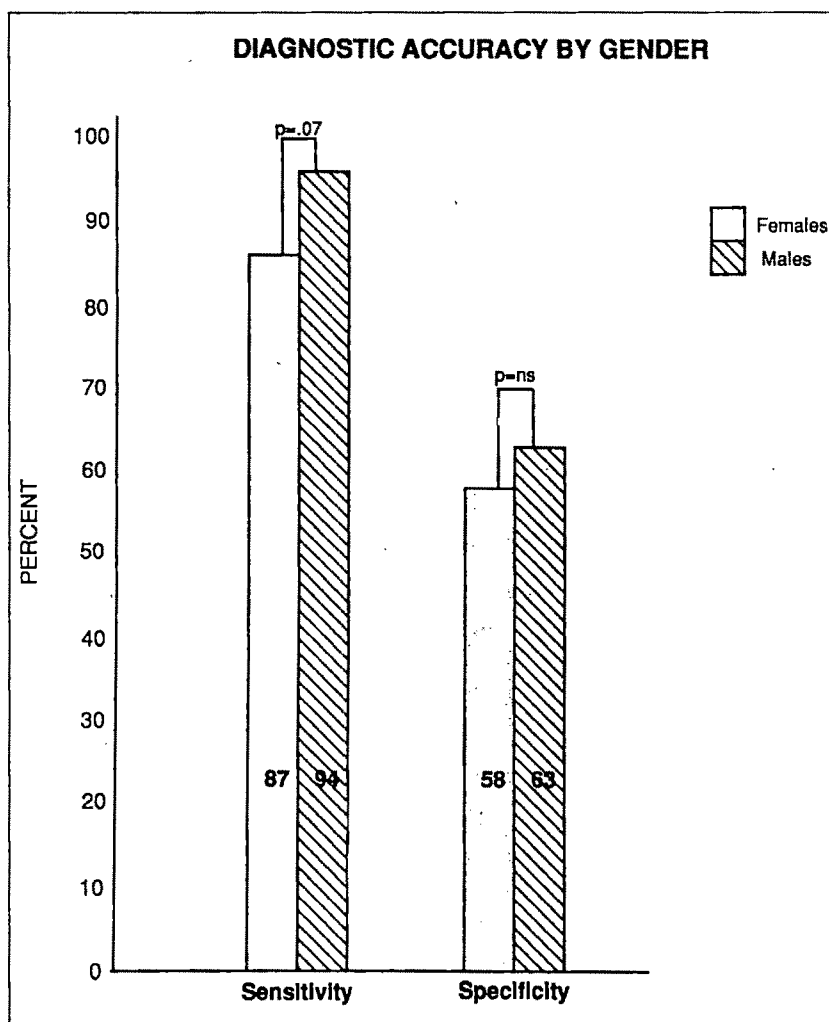
FIGURE 2. The sensitivity and specificity of dipyridamole thallium testing is comparable between the sexes.

SENSITIVITY STRATIFIED BY EXTENT OF CAD

FIGURE 3. In the subgroup with 1-vessel disease (SVD) the sensitivity for detection of disease was greater in men. CAD = coronary artery disease; other abbreviations as in Figure 1.
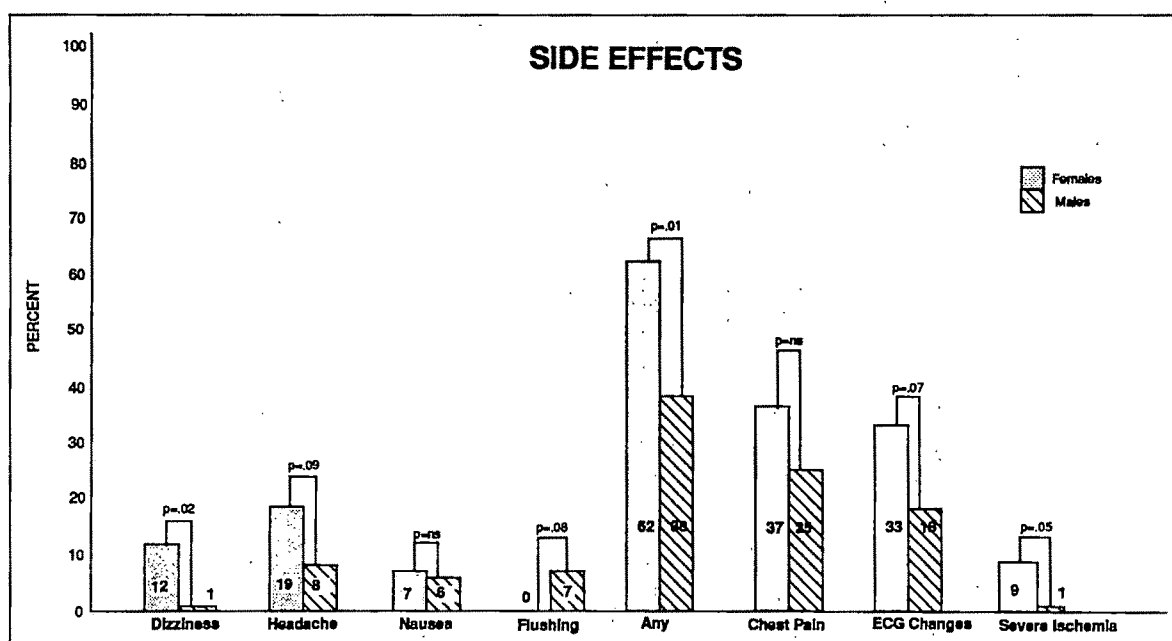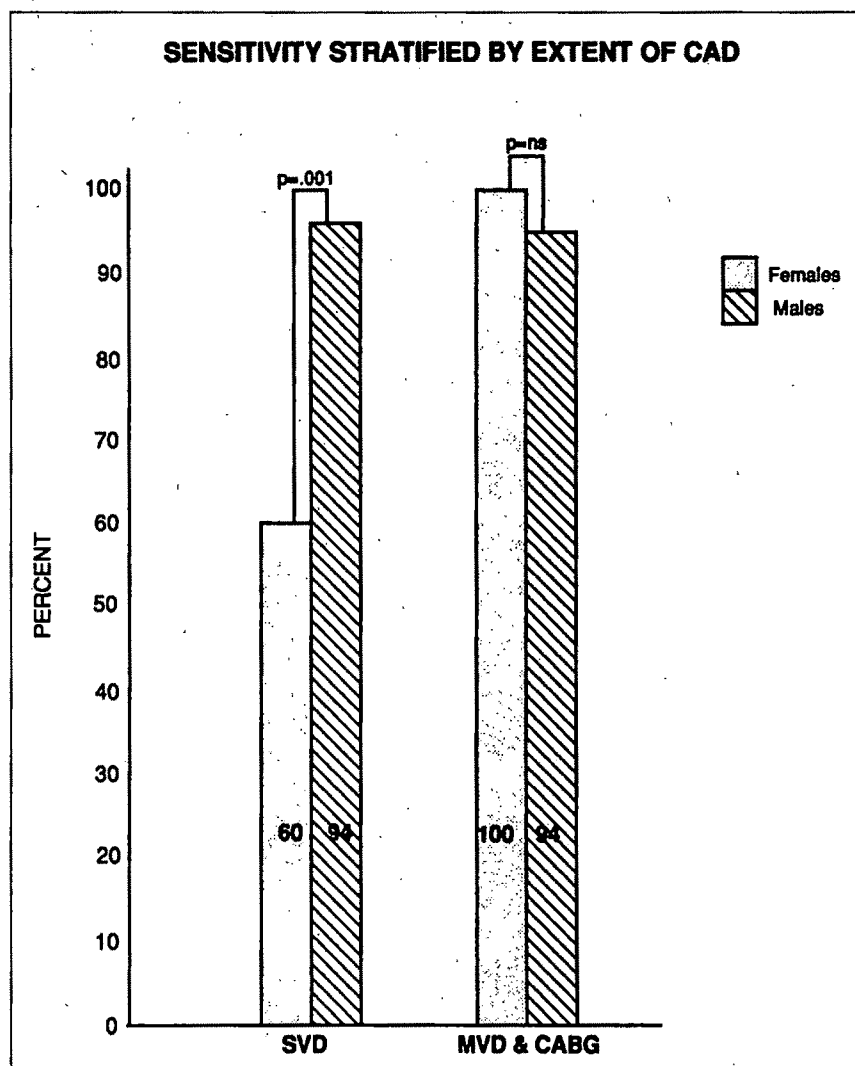
SIDE EFFECTS

FIGURE 4. Women had more adverse effects than men. Severe ischemia and dizziness were more common in women. ECG = electrocardiographic.

cant difference between the sensitivity for the detection of multivessel CAD (with or without coronary artery bypass grafting): 1.0 (21 of 21) in women compared with 0.94 in men (44 of 47).

Of the four women with false-negative dipyridamole thallium-201 scans, 3 had stenoses in a distal or branch coronary vessel. Four men had false-negative scans: 2 had distal coronary artery or branch vessel disease and the other 2 had patent coronary artery bypass grafting. Four of 8 scans classified as false-positive had a ≥30% diameter stenosis in 1 or more coronary arteries. One additional patient had a myocardial bridge, whereas 2 patients had normal angiograms.

Adverse effects: The overall incidence of adverse effects was 62% (27 of 43) in women and 38% (27 of 71) in men (p <0.01). The incidences of chest pain, ischemic electrocardiographic changes, headache, nausea and flushing did not differ significantly between the sexes (Figure 4). There was a greater incidence of dizziness in women. Four women (9%) experienced severe ischemia, defined as recurrent or prolonged (>15 minutes) chest pain associated with significant electrocardiographic ST-segment changes, compared with only 1% (1) of men.

Aminophylline or nitroglycerin requirement: Noncardiac symptoms were treated with intravenous aminophylline if severe. Aminophylline was used to treat chest pain, with or without ischemic electrocardiographic changes in 9 of 43 women (21%) and in 12 of 71 men (17%) (p = NS). Six male (8%) and 5 female (12%) subjects also received nitroglycerin (p = NS). One female patient with recently controlled unstable angina did not respond quickly to intravenous aminophylline and sublingual nitroglycerin. This patient required emergency angioplasty of a proximal left anterior descending stenosis, and did not develop evidence of a myocardial infarction.

DISCUSSION

The diagnostic accuracy of exercise testing is reduced in many patients with neurologic, rheumatologic or vascular problems that restrict treadmill or bicycle ergometer testing. Preoperative noninvasive diagnosis of CAD has been shown to be useful in selected subsets of patients.[7-10] Use of pharmacologic vasodilator agents that increase coronary perfusion and accentuate the difference in flow between angiographically normal vessels and those with flow-limiting stenoses has been successful in detecting CAD. Intravenous dipyridamole increases coronary blood flow up to 4 times when administered in a dose of 0.14 mg/kg/min,[5] and when used in conjunction with thallium-201 has been found to be a safe and accurate diagnostic and prognostic test for CAD.[11,12]

Diagnostic accuracy: Our data demonstrate that intravenous dipyridamole thallium-201 myocardial imaging has acceptable sensitivity for detection of CAD in both sexes. Sensitivity for detection of 1-vessel disease was lower in women than in men; however, this patient subset was relatively small. Careful consideration of breast attenuation artifact, particularly in the antero-

septal, anterior and anterolateral areas, as well as the basal posterolateral region, is critical.[13] The distribution of disease between major coronary arteries was not statistically significant between the sexes in this study (Table III). Defects were distributed in the posterolateral (2) inferoapical (2) and anterolateral (1) regions in women, and in the inferior (1), anterolateral (1), anteroseptal (1) and apical (2) area in men. Thus, breast attenuation artifact was not an adequate explanation for the sex-based differences in our diagnostic finding.

Specificity was relatively low compared with other studies, attributable (in part) to post-test bias. Cardiac catheterization was frequently performed in patients with abnormal test results, whereas those with negative test results were usually not referred for diagnostic angiography. Additionally, dipyridamole thallium-201 testing used as a screening test for CAD favors sensitivity over specificity.

Side-effect profile: Our data confirm that intravenous dipyridamole thallium-201 imaging is safe at a standard dose of 0.56 mg/kg body weight.[4,12,14] A greater incidence of adverse effects was experienced in response to dipyridamole in women. Dipyridamole is known to have a volume of distribution similar to that of a purely water soluble compound, antipyrine, and is thus considered to be a water soluble compound.[15] Dipyridamole is dosed according to body weight, not lean body mass or ideal body weight. Although not calculated in this or larger[11] registry studies, women generally have greater fat-to-muscle ratios than men, and would therefore tend to have a relatively smaller volume of distribution for dipyridamole. Our group has previously demonstrated an increased incidence of adverse effects in obese patients, which is also compatible with this theory.[14]

Clinical implications: Dipyridamole thallium-201 imaging is a safe, noninvasive method for the evaluation of patients with CAD. In a relatively small subset, there was a trend toward a lower sensitivity for detection of 1-vessel disease in women than in men. This finding requires validation in a larger patient population. The incidence of any dipyridamole side effect and of dizziness and severe ischemia is greater in women than in men. Although the cause of this gender difference is undetermined, consideration should be given to reducing the dose of intravenous dipyridamole because of the theoretically smaller volume of drug distribution in women.

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Strategy of Complete Revascularization in Patients with Multivessel Coronary Artery Disease (A Report from the 1985–1986 NHLBI PTCA Registry)

Martial G. Bourassa, MD, Richard Holubkov, MS, Wanlin Yeh, MA, Katherine M. Detre, MD, DrPH, and the Co-investigators of the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry*

Percutaneous transluminal coronary angioplasty (PTCA) is increasingly performed in patients with multivessel coronary artery disease (CAD) despite reports showing relatively low rates of complete revascularization and poorer long-term prognosis for patients with significant residual narrowings. Reasons for incomplete revascularization were assessed in 618 patients with multivessel CAD in the 1985–1986 National Heart, Lung, and Blood Institute (NHLBI) PTCA Registry. The PTCA operator was asked to describe the treatment plan and outcome for each of the 1,942 significant lesions (≥50% luminal diameter stenosis) in the Registry patients. Although all significant narrowings were considered amenable to balloon angioplasty in 77% of patients, complete correction was intended only for 34% of them. It was attempted in 28% and successful in 19%. Only 63% of total occlusions were considered amenable to PTCA and only 54% of those attempted were successfully dilated. PTCA was intended for 38% with 50 to 69% stenoses versus 80% with 70 to 89% stenoses and for >85% with narrowings ≥90%. Dilatation in narrowings of the left circumflex and left anterior descending artery systems was intended less frequently than in lesions of the right coronary artery. Finally, there was wide variability in operator strategy among the different Registry sites. It is concluded that (1) complete revascularization is infrequent after PTCA in patients with multivessel CAD, (2) major reasons for incomplete correction include total occlusions that are not PTCA amenable or are unsuccessfully attempted, and less than severe (50 to 69%) coronary narrowings by visual estimation for which PTCA is frequently not in- tended, and (3) incomplete revascularization is often part of the PTCA strategy, and can usually be predicted before PTCA.

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When introduced in 1977, percutaneous transluminal coronary angioplasty (PTCA) was performed primarily in patients with single discrete narrowings.[1] As operator experience increased and the relevant technology improved, the procedure was increasingly applied to patients with multivessel coronary artery disease (CAD).[2] Some patients, through failure of the procedure or because not all stenoses are attempted, are left with significant residual lesions. Several studies reported relatively high rates of incomplete revascularization after balloon coronary angioplasty in patients with multivessel CAD, and some have suggested a poorer long-term prognosis for patients with residual CAD.[3-10] However, identification of the possible causes for incomplete revascularization was rarely attempted in these studies. This report presents the 1985–1986 National Heart, Lung, and Blood Institute (NHLBI) PTCA Registry data on completeness of revascularization in patients with multivessel CAD, and endeavors to explain why complete revascularization was frequently not achieved after PTCA in these patients.

METHODS

Patient population: We considered in this report a cohort of 1,802 patients from 15 participating sites who underwent PTCA outside of the setting of a recent myocardial infarction (within the last 10 days). Of these patients, 964 had significant multivessel CAD (≥50% luminal diameter stenosis) in 2 or 3 coronary territories as defined by the Coronary Artery Surgery Study algorithm.[11] Because presence of bypass grafts and significant left main stenosis can confound the assessment of CAD and affect PTCA strategy, we deleted 222 Registry patients who had prior bypass surgery or left main CAD at the time of their first PTCA from analysis.

For the sake of clarity, we excluded from this analysis an additional 124 patients with a left dominant coronary artery system. In patients with a left dominant system, narrowing in the right coronary artery is not

counted as significant by the Coronary Artery Surgery Study algorithm (even though some Registry patients actually had such lesions attempted), and it is possible for a patient to have multivessel CAD with only 1 significant lesion. Only patients with a balanced or right dominant anatomy were included, because in these cases 2- and 3-vessel CAD are defined by the presence of at least 1 significant narrowing in each of 2 or 3 of the major coronary artery systems, respectively. Thus, 618 patients with right or balanced dominance and significant CAD in multiple arteries remained for analysis. For these patients, 2- or 3-vessel CAD was determined by whether 2 or 3 of the coronary territories (right coronary, left anterior descending and left circumflex arteries), respectively, had significant CAD.

Definitions: Baseline data collection in the PTCA Registry have been previously described.[2] During baseline angiographic data collection, the PTCA operator was asked to describe the treatment plan for each significant lesion as 1 of the following: PTCA amenable and intend to dilate, PTCA amenable but do not intend to dilate, and not PTCA amenable. Information was also collected about which intended stenoses were attempted, and which of these were successfully dilated.

Angiography was performed with multiple views before and after PTCA. The extent of stenosis before and after PTCA was determined by the operator's evaluation, using the view that showed the most severe stenosis. The definitions of baseline and early postangioplasty residual vessel disease recorded in the Registry used the Coronary Artery Surgery Study algorithm, with a 50% cutpoint for significant disease.

Because the Registry did not collect detailed morphologic information on lesions that were not attempted, it was only possible to break down the analysis of significant lesions by severity of stenosis before angioplasty and lesion location.

RESULTS

Baseline characteristics and in-hospital events: Table I lists the baseline characteristics and in-hospital complications of the 618 patients in this study by number of diseased vessels. Patients with 3-vessel CAD were somewhat older, more likely to be women, and had a more frequent history of congestive heart failure and a significantly more frequent history of diabetus mellitus than patients with 2-vessel CAD.

Multiple lesions were attempted during PTCA in 59% of patients and multivessel angioplasty was performed in 46%. As expected, there were more multilesion and multivessel attempts in patients with 3- than in patients with 2-vessel CAD. About 20% of procedures were performed on an urgent or emergency basis, which meant that in the operator's judgment, revascularization had to be accomplished before the patient could be discharged from the hospital. Rates of major events occurring during or after PTCA in the hospital were 1.6% for mortality, 5.5% for myocardial infarction, and 4.4% for emergency coronary bypass surgery.

Operator strategy and reasons for incomplete revascularization: Whereas 77% of patients with mul-

TABLE I Baseline and PTCA Characteristics and In-Hospital Events

Characteristics	Two-Vessel Disease (n = 447) %	Three-Vessel Disease (n = 171) %	Total (n = 618) %
Mean age (years)	59	60	59
Age ≥ 65 years	30	36	32
Women/men	27/73	35/65	29/71
Unstable angina pectoris	52	59	54
Ejection fraction < 50%	20	20	20
Prior myocardial infarction	43	40	43
Congestive heart failure (history)	4	8	5
Diabetes mellitus (history)*	11	21	14
Systemic hypertension (history)	47	54	49
Multiple lesion angioplasty†	57	66	59
Multivessel angioplasty*	42	54	46
Urgent/emergency angioplasty	19	21	19
In-hospital death	1.1	2.9	1.6
Myocardial infarction	5.4	5.8	5.5
Emergency coronary bypass surgery	4.0	5.3	4.4
Elective coronary bypass surgery	2.7	5.3	3.4

*p <0.01 for chi-square test comparing patients with 2- and 3-vessel disease; †p <0.05.
PTCA = percutaneous transluminal coronary angioplasty.

tivessel disease in the 1985–1986 PTCA Registry were considered to be amenable to complete revascularization by balloon coronary angioplasty alone, complete correction was intended for only 34% of them. This figure was 39% for 2- and 21% for 3-vessel CAD. Complete revascularization was attempted in 33%, and achieved in 23% of patients with 2-vessel CAD and in 15 and 9% of patients with 3-vessel disease (Table II). Although complete revascularization was achieved approximately twice as often in patients with 2-vessel as in patients with 3-vessel CAD, it was achieved in 68 and 62% of the time, respectively, when it was actually planned and attempted.

Operator strategy and reasons for incomplete revascularization for all patients are shown in Figure 1. Not all lesions were amenable to PTCA in 24% of patients, and PTCA was considered possible but was not intended at the operator's discretion in 42% of patients. Only 6% of patients in whom complete revascularization was intended did not have all lesions attempted. Finally, the procedure was technically unsuccessful in 9% of patients.

Influence of lesion severity and location on percutaneous transluminal coronary angioplasty strategy: Table III compares lesion severity and location with operator strategy and outcome. Only 63% of total occlusions were considered amenable to PTCA, compared with 94 to 95% for 50 to 99% stenoses. Lesions of the left circumflex artery were slightly less frequently amenable than stenoses of the right and left anterior descending artery.

Among lesions suitable for PTCA, the procedure was intended for 38% with stenoses of 50 to 69%, compared with 80% with narrowings of 70 to 89%, and >85% with lesions ≥90%. Of the 3 locations, dilatation was most frequently planned for lesions in the right coronary artery.

Variability by Registry site: Table IV illustrates the marked variability in operator strategy and outcome among the different NHLBI PTCA Registry sites. The percentages of all patients in whom complete revascularization was amenable, intended, attempted and achieved by balloon angioplasty varied from 46 to 92%,

TABLE II Operator Strategy and Outcome Per Patient

	Two-Vessel Disease (n = 447)		Three-Vessel Disease (n = 171)		Total (n = 618)	
	No.	%	No.	%	No.	%
Amenable to complete revascularization	351	79	122	71	473	77
Intended complete revascularization	176	39	35	21	211	34
Attempted complete revascularization	148	33	26	15	174	28
Achieved complete revascularization	101	23	16	9	117	19

TABLE III Operator Strategy and Outcome by Lesion Severity and Location

	Total No.	No. Amenable	% Amenable of Total	No. Intended	% Intended of Amenable	No. Attempted	% Attempted of Intended	No. Dilated to <50%	% of Attempted Dilated to <50%
All lesions	1,942	1,754	90	1,263	72	1,176	93	951	81
Severity of stenosis									
50–69%	459	433	94*	165	38*	150	91	141	94*
70–89%	672	638	95	508	80	465	92	399	86
90–99%	559	524	94	454	87	431	95	341	79
100%	252	159	63	136	86	130	96	70	54
Artery									
Right coronary	631	580	92†	464	80*	438	94	356	81
Left anterior descending	778	710	91	496	70	458	92	371	81
Left circumflex	533	464	87	303	65	280	92	224	80

*p <0.001; †p <0.05.
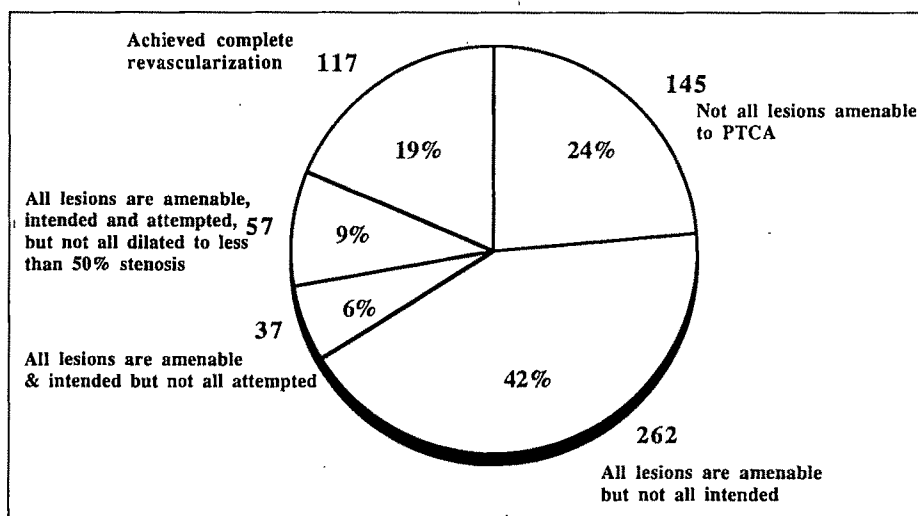
FIGURE 1. Operator strategy and reasons for incomplete revascularization for the total group of patients with multivessel coronary artery disease (n = 618): (1) not all lesions amenable to percutaneous transluminal coronary angioplasty (PTCA) (n = 145); (2) all lesions amenable but not all intended (n = 262); (3) all lesions amenable and intended but not all attempted (n = 37); (4) all lesions amenable, intended and attempted but not all dilated to <50% stenosis (n = 57); and (5) achieved complete revascularization (n = 117).

	Site A (n = 31)	Site B (n = 111)	Site C (n = 72)	Site D (n = 146)	Site E (n = 26)	Site F (n = 54)	Site G (n = 57)	Site H (n = 33)	Site I (n = 38)	Other Sites* (n = 50)	All Patients (n = 618)
Amenable to complete revascularization (%)	71	87	47	89	46	50	84	88	92	78	77
Intended complete revascularization (%)	52	61	29	23	8	9	44	15	21	54	34
Attempted complete revascularization (%)	39	55	24	17	4	9	39	15	18	38	28
Achieved complete revascularization (%)	26	38	13	12	0	7	26	9	16	26	19

*Sites contributing <25 patients are combined in this category.

8 to 61%, 4 to 55%, and 0 to 38%, respectively. Among 2 of the sites with the lowest intent for complete revascularization, 1 site performed PTCA mostly on right coronary artery lesions, and the other site did not plan to dilate lesions between 50 and 60%.

DISCUSSION

Currently, PTCA is widely accepted as the revascularization procedure of choice in symptomatic patients with 1-vessel CAD because of its high potential for complete angiographic correction[2,3] and global relief of angina and myocardial ischemia.[12,13] In contrast, complete correction is achieved much less frequently after PTCA in patients with multivessel CAD. As demonstrated in this report, complete revascularization was accomplished in approximately 20% of patients with multivessel CAD in the 1985-1986 NHLBI PTCA Registry, including approximately 25% of patients with 2-vessel CAD, and only 10% of patients with 3-vessel CAD. In recent studies in which the degree of revascularization was evaluated in patients with multivessel disease undergoing PTCA, complete revascularization was reported to vary from 20 to 59%.[5-10] In general, these complete revascularization rates were significantly higher for patients with 2-vessel than for patients with 3-vessel CAD, and highest in reports in which most patients had 2-vessel CAD.

Reasons for incomplete revascularization were not analyzed in these previous studies. The design of the NHLBI PTCA Registry lent itself to a well-defined systematic breakdown for some of the major reasons for incomplete revascularization in patients with multivessel CAD. Detailed analyses revealed that, even before undertaking the procedure, complete revascularization was clearly not possible or was not planned for the majority of Registry patients with multivessel CAD. When the suitability of all lesions and the plan of the operator are taken into account, we find that complete revascularization was attempted and achieved in 57 and 46% of patients with 2- and 3-vessel CAD, respectively.

The Registry database suggests that the majority of lesions not amenable to PTCA are total occlusions, whereas many of the lesions amenable but not intended have moderate but not severe stenosis.

One or more chronic total occlusions are present in a significant number of patients with multivessel CAD

and they are often considered not to be amenable to PTCA, unless they are presumed to be recent, e.g., <3 months old. In the NHLBI PTCA Registry, the operator did not indicate whether he believed that the occlusion was recent or older. Overall, in 63% of the time, occlusions were considered to be potentially suitable for PTCA. However, the success rate for attempted occlusions was only 54%.

Although moderate but not severe stenoses were considered suitable for PTCA in a very high percentage of cases (94 to 95%), the operator often did not plan to perform angioplasty on these lesions. PTCA was intended for only 38% of stenoses between 50 and 69% for 80% of stenoses between 70 and 89%, and for >85% of stenoses ≥90%. There are several possible reasons why in patients with multivessel CAD, the Registry operators chose not to attempt PTCA in less severe coronary stenoses.[12,13] Major complications after PTCA are often unpredictable and can occur in less severe lesions, dilatation of the most severe lesions, the so-called culprit lesions, often leads to relief of angina and myocardial ischemia, moreover, a second procedure at a later date, after documentation of residual ischemia or angina, is always possible. Restenosis after dilatation of a moderate lesion, when it occurs, may be more severe than the initial lesions.

The differences in the percentages of patients in whom complete revascularization was intended at the Registry sites reflect the varying levels of aggressiveness in the practice of PTCA therapy as well as variations in the patients' clinical and angiographic characteristics. Differences in revascularization strategy that exist between the Registry sites can also be seen among other interventional laboratories and may explain variations in the results of follow-up studies comparing patients with complete and incomplete revascularization.[5-10] A more detailed report of revascularization strategy, perhaps along the lines of this report, may help to clarify results and facilitate comparison between studies.

The results published here reflect the state of PTCA strategy for multivessel CAD in experienced centers in 1985 and 1986. With subsequent improvements in PTCA equipment and promising new devices, it would be interesting to compare current approach to completeness of revascularization with the pattern described in this report.

APPENDIX

The following persons and institutions participated in the NHLBI 1985–1986 PTCA Registry.

Clinical centers: Boston University Medical Center: Principal Investigator, David P. Faxon, MD; Data Coordinator, Madeline Erario; Emory University Hospital, Atlanta: Principal Investigator, Spencer B. King III, MD; Data Coordinator, Cynthia Sutor; Georgetown University Hospital, Washington, DC: Principal Investigator, Kenneth M. Kent, MD; Data Coordinators, Carolyn Ewels, Katie Kehoe; Massachusetts General Hospital, Boston: Principal Investigator, Peter C. Block, MD; Data Coordinator, Elizabeth Block; Mayo Clinic, Rochester, Minn.: Principal Investigator, David R. Holmes Jr., MD; Data Coordinators, LaVon Hammes, Suzy Brevig; Medical Center Hospital, Houston: Principal Investigator, Mahdi Al-Bassam, MD; Data Coordinator, Debbie Lance; Medical College of Pennsylvania, Philadelphia: Principal Investigator, Lamberto G. Bentivoglio, MS, MD; Data Coordinator, Eileen Shappell; Medical College of Virginia, Richmond: Principal Investigator, Michael J. Cowley, MD; Data Coordinator, Kim Kelly; Miami Heart Institute: Principal Investigator, Arthur J. Gosselin, MD; Data Coordinator, Hazel Yon; Montreal Heart Institute: Principal Investigator, Martial G. Bourassa, MD; Data Coordinator, Suzanne Morin; National Heart, Lung, and Blood Institute, Bethesda, MD: Principal Investigators, Richard O. Cannon, MD, Martin Leon, MD; Data Coordinator, Rita Mincemoyer; Seton Medical Center, Daly City, CA: Principal Investigators, Richard K. Myler, MD, Simon H. Stertzer, MD, David A. Clark, MD; Data Coordinator, Mary Murphy; Rhode Island Hospital/Brown University, Providence, R.I.: Principal Investigator, David O. Williams, MD; Data Coordinator, Shirley Emin; St. Francis Regional Medical Center, Wichita, KS: Principal Investigator, Joseph P. Galichia, MD; Data Coordinator, Jan Meires; St. Luke's Episcopal Hospital, Houston, TX: Principal Investigator, Louis L. Leatherman, MD; Data Coordinator, Joan Matties; St. Luke's Hospital, Milwaukee, WI: Principal Investigator, Gerald Dorros, MD; Data Coordinators, Lynne Janke-Mathiak, Marla Engel.

Data coordinating center: University of Pittsburgh: Principal Investigators, Katherine M. Detre, MD, DrPH, Sheryl F. Kelsey, PhD; Statisticians, John Wilson, PhD, Richard Holubkov, MS, Ann Rodewald Steenkiste, MS, Ann Lu, MS; Manager (systems analysis), William P. Amoroso; Programmer, Sheela Ghosal; Data Manager, Verna Niedermeyer; Research Assistants, Polly Swanson, Sharon Yeh, Huiman Xia Barnhart; Administrative Secretaries, Donna Gibbons, Margaret Jasko; Secretary, Rita Wolk.

National Heart, Lung, and Blood Institute: Eugene R. Passamani, MD, and George Sopko, MD (program office), Bethesda, MD.

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Mortality After Coronary Angioplasty and Coronary Artery Bypass Surgery (The National Medicare Experience)

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Mortality rates for Medicare patients who underwent coronary artery bypass surgery were compared with those who had angioplasty or angioplasty and bypass surgery. Two data sets were used for this study: The first contained information on demographic factors, co-morbidities and subsequent mortality on all 96,666 Medicare patients who had bypass surgery or angioplasty in 1985; the second contained additional detailed clinical data collected using the MedisGroups method on a random sample of 2,931 revascularization patients from 6 states.

From the national data set 30-day and 1-year mortality rates were 3.8 and 8.2% for 25,423 angioplasty patients and 6.4 and 11.8% for 71,243 bypass surgery patients (p <0.001 for both time periods). Mortality rates for the MedisGroups data were 4.4 and 8.5% for the angioplasty patients and 6.5 and 11.9% for the bypass surgery patients. After eliminating patients admitted with a myocardial infarction, mortality rates were 1.9 and 6.0% for 632 angioplasty patients and 5.1 and 10.8% for 1,730 bypass surgery patients. The risk-adjusted relative risk of mortality for bypass surgery versus angioplasty was 1.72 (p = 0.001) for all patients, 2.15 (p <0.001) for low-risk patients and 0.90 (p = not significant) for high-risk patients. Results suggest that low-risk patients have better survival with angioplasty because of lower short-term mortality.

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Studies to evaluate new technologies are usually conducted in an academic institution[1-3] or by a group of collaborating institutions with a research orientation.[4-6] Although these institutions have the personnel with the training and motivation to conduct large studies, their patients, technical expertise and environments may not be representative of the medical system as a whole. If they are not representative, then technology assessment in these institutions may indicate efficacy (the performance of the technology in ideal settings) but not effectiveness (the performance of the technology in the population actually subjected to the technology). Therefore, study results from academic institutions may not provide optimal information needed for decision making by physicians or policy planners.

The Health Care Financing Administration (HCFA) is investigating methods to obtain information on the effectiveness of medical strategies from routinely collected data.[7] The billing data collected at the present time are adequate for some assessments and plans are underway to collect detailed clinical data on 10% of Medicare patients[8] that can be used for more sophisticated assessments. Other routinely collected detailed clinical data bases such as the Duke cardiovascular registry[2] or the MedisGroups comparative data base[9] can also be analyzed for the study of effectiveness. These observational data bases have greater potential for biases than randomized clinical trials for treatment evaluation. On the other hand, the observational data bases are often less expensive and more timely than randomized trials, and they are more likely to contain the patients actually receiving the technology. For these reasons observational studies provide information that is complementary to that provided in trials.

In a pilot project to determine the value of routinely collected data, HCFA has used a modified version of the MedisGroups system[9] to collect data on patients undergoing a coronary artery revascularization procedure: bypass surgery or angioplasty. A preliminary analysis of these data was included in a previous publication.[7] The present report evaluates further how these data can be used to compare survival after coronary artery percutaneous transluminal angioplasty (PTCA) and coronary artery bypass grafting (CABG).

METHODS

Patients who underwent both PTCA and CABG during the same hospitalization were classified as having PTCA because it was most likely the admission procedure. Classifying patients with CABG and PTCA as

having PTCA is also a conservative approach because it reduces the differences in survival between the 2 procedures.

Two data sets were analyzed in this study. The first contained information from the UB82 hospital claims data for all patients who had a procedure billed to HCFA under Medicare in 1985. Information available from the claims data included ICD-9-CM codes on as many as 5 diagnoses and 3 procedures, and the patients' race, sex and age. Additional information on the date of death for all of these patients who died before January 1, 1987 was obtained from the Social Security Administration. A study published in 1983[10] reported that the social security information on mortality identified 93.8% of the deaths in 1979 to 1980 and incorrectly labeled people as dying within 0.2% of the time. The results had been improving up to 1980 and may be better now than at that time.

The second data set contained detailed clinical information obtained by the HCFA from the medical records of Medicare patients having CABG or PTCA hospitalized in 1985. Seven peer review organizations participated in the data collection. Each peer review organization randomly selected approximately 600 revascularization patients for abstraction from the pool of patients who had billed Medicare for PTCA or CABG. Sample sizes were reduced for each of the peer review organizations because charts could not be located. The sample sizes from each peer review organization were Alabama (n = 593), Arizona (n = 483), Indiana (n = 512), Pennsylvania (n = 476), Utah (n = 317) and Wisconsin (n = 540) for a total of 2,921 patients. Utah had fewer patients because there were insufficient numbers of Medicare patients who had a revascularization procedure. To increase the sample size from Utah some patients were added from 1986. Data were also collected from New York, but these were not analyzed for reasons discussed below.

The extraction of data from the hospital medical record of patients in the second data set was performed by coders trained by MediQual to use the MedisGroups proprietary method for abstracting the medical record. The MedisGroups method has the capacity to obtain 550 items of important clinical information referred to as key clinical findings. The key clinical findings include admission symptoms, history, the results of preadmission tests documented in the medical record (e.g., angiography), physical examinations (including vital signs), and laboratory and specialized diagnostic tests. Key clinical findings are not abstracted from emergency room records or data obtained during resuscitation efforts, and this study only utilized key clinical findings collected before the revascularization procedure or on the first 2 days of hospitalization if the revascularization procedure was delayed >2 days. Only abnormal findings are recorded by MedisGroups. Therefore no distinction could be made between normal findings and findings not sought. Only variables that were abnormal for at least 1% of either group of revascularization patients were included in the analysis.

In addition to the key clinical findings collected by the MedisGroups system, a severity of illness score derived by MedisGroups algorithms from these findings was also available. The algorithms assign each clinical finding to a severity group from 0 to 4 that represents the potential of organ failure. A score of 1 indicates a slight potential for organ failure and a score of 4 indicates the presence of organ failure. Based on the highest severity scores and the number of key clinical findings with these scores, the algorithm then assigns the patient to an admission severity group from 0 to 4. A detailed description of the admission severity group score is presented by Brewster et al.[9] For the present study we considered patients having admission severity group scores of 2, 3 or 4 as high risk.

The MedisGroups information was supplemented by information on up to 30 ICD-9-CM diagnostic codes and 30 procedure codes. Procedures of particular interest included aortic valve replacement, and ventricular resection as risk factors for the CABG patients.

The outcome variable used for these patients was whether or not the patient had died prior to January 1987 as determined by data from the Social Security Administration. The median follow-up time for the patients in this study from the date of admission until this date was 551 days (about 18 months), range 260 to 719 days.

Patients were classified into the PTCA or CABG group on the basis of the ICD-9 procedure codes. Unfortunately, in 1985 and 1986 when these data were recorded, the ICD-9 codes were the same for patients who had coronary artery PTCA or coronary artery endarterectomy. For this reason it was necessary to review the medical records of all patients who had both procedures coded. This required the participation of the state peer review organizations. The New York peer review organization did not participate in helping us to obtain the information, and therefore, data from all New York patients were excluded from the analyses. Data from 1 hospital in Pennsylvania were also withdrawn from the analysis because this hospital did not verify their medical records.

To compare the results of CABG and PTCA, we eliminated from the analysis patients who had a cardiac arrest or evidence of a myocardial infarction before the procedure. Evidence of a myocardial infarction included a principal diagnosis of a myocardial infarction, or pre-procedure evidence of infarction from electrocardiographic findings or creatine kinase or creatine kinase-MB fraction enzymes.

The optimal risk adjustment necessary for the analyses in this study requires information on all cardiovascular risk factors as established by the Duke cardiovascular data registry[2,11] and others.[12-15] These risk factors include indicators of cardiac damage and function, coronary anatomy, severity of the angina, conduction defects, age, sex and mitral regurgitation. The risk factors not available in the MedisGroups data base will only affect the comparisons of CABG and PTCA if they are more prevalent for patients having one of the procedures than the other and are not strongly associated with risk factors that are measured. The principal risk factor not included in this study that is likely to affect the comparisons of the procedures is the presence of left

TABLE I Comparison of Study Data* and National Data				
	PTCA		Bypass	
	Study	National	Study	National
No. of pts.	858	25,423	2,063	71,243
No. of hospitals	88	816	80	671
Average age (yrs)	68.4	68.7	69.0	69.4
% aged <65 years	13.6	13.4	13.1§	11.6
% women	35.5	38.4	28.3‖	31.2
% black	2.3	2.9	1.6‖	2.5
PTCA and bypass—same admission	11.9†	10.7‡		
Length of stay				
Mean ± SD	8.0 ± 7.1	7.8 ± 7.2	14.4¶ ± 9.1	15.4 ± 11.0
30-day mortality (%)	4.4	3.8	6.5	6.4
1-year mortality (%)	8.5	8.2	11.9	11.8

*The study data are random samples of Medicare patients from 6 states.
†Based on both bypass and PTCA coded among 30 listed procedures. PTCA was verified by review of the medical record.
‡Based on both bypass and PTCA coded among 3 listed procedures. In these data, PTCA could not be distinguished from coronary artery endarterectomy.
§p <0.05; ‖p <0.01; ¶p <0.001 for the difference between study data and national data.
PTCA = percutaneous transluminal coronary angioplasty.

main coronary artery disease. We used published reports to determine the potential effect of left main disease on the results of this study.

Statistical analyses: The purpose of the statistical analyses was to compare patient survival for the 2 procedures after adjusting for differences in patient characteristics. The analysis was in 4 stages: (1) A univariate chi-squared test was used to identify clinical abnormalities on admission associated at the p <0.10 level with 1-year mortality rates for either of the procedures. (2) These abnormalities were included in a stepwise Cox proportional-hazard regression analysis of the combined data set to derive a final regression equation for predicting mortality. (3) An indicator variable for procedure was added to this equation to determine if the mortality rate differed between the 2 revascularization procedures after adjusting for patient characteristics. Indicator variables were also added to determine if there was an interaction effect between CABG and any patient characteristic. (4) Patient survival before 60 days was compared for the 2 procedures by censoring all subjects at 60 days. To compare survival after 60 days, we eliminated subjects who died before 60 days.

RESULTS

Table I lists characteristics of all the PTCA and bypass patients in each of the data sets: (1) the sample of Medicare patients with MedisGroups clinical information; and (2) all Medicare patients in the United States. Both the demographic characteristics and the results of surgery were similar for the groups, suggesting that patients in the sample appear to be representative of all Medicare patients in the United States.

The remainder of the analyses was performed only on the MedisGroups data after excluding patients who had a cardiac arrest or evidence of a myocardial infarction before the procedure. We could not compare the national data with our data set for patients who did not have a myocardial infarction because the method for

identifying patients with myocardial infarction for elimination could not be applied to the national data.

Figure 1 shows the survival curve for patients with PTCA to be significantly higher than the curve for patients with CABG (p <0.01 using the log rank test). The 30-day and 1-year mortality rates were 1.9 and 6.0% for the 632 PTCA patients and 5.1 and 10.8% for the 1,730 CABG patients (p <0.01 for both time periods). For the 60 PTCA patients who underwent CABG, the 30-day and 1-year mortality rates were 8.3 and 10.0%. Mortality in 9.5% of the PTCA patients who had CABG accounted for 41.7% of the 30-day mortality and 15.8% of the 1-year mortality of the PTCA patients.

The frequencies of the principal findings and the clinical differences between the patients in the 2 revascularization groups are listed in Table II. Factors signif-
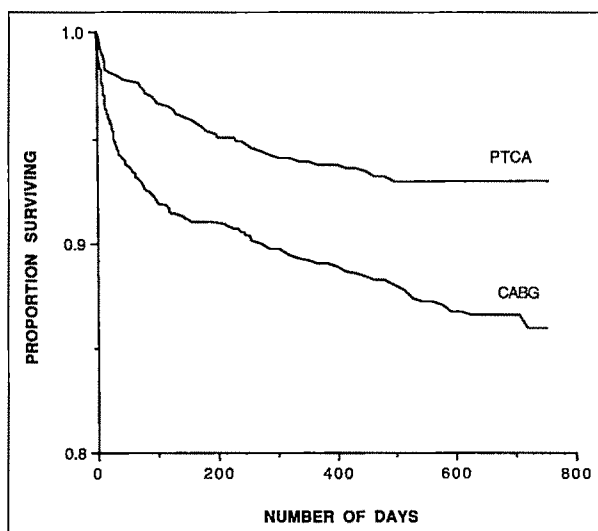
FIGURE 1. Survival curves for patients who had percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG).

icantly related to choice of procedure in a multivariate logistic regression analysis are indicated. In general CABG patients were at higher risk than PTCA patients. This is shown overall by the odds of 2.4 of a CABG patient having a high risk MedisGroups severity score than a PTCA patient. In addition CABG patients were more likely to have evidence of congestive heart failure (by x-ray, by S_3 gallop and by history), a history of myocardial infarction, and evidence of cardiac impairment as defined in the Methods section. Patients were more likely to have PTCA if they had only 1-vessel disease, had a previous revascularization procedure, were women, or had an elevated partial thromboplastin time indicating treatment with heparin for unstable angina.

The results in Table II suggest that CABG patients may have had higher mortality rates than PTCA pa-

tients partly because they were at greater risk of mortality before the procedure. Figure 2 shows survival curves for subjects divided into high- and low-risk groups as defined by the admission severity group score. The high-risk subjects had a much higher mortality rate than the low risk subjects. The 1-year mortality rate was 19.8% for the 76 high-risk PTCA patients and 17.0% for the 430 high-risk CABG patients. In the low-risk patients, the 1-year mortality was 4.2% for 556 PTCA patients and 8.7% for 1,300 CABG patients. There was no significant difference between the revascularization groups for the high-risk patients, but among the low-risk patients the PTCA patients had a significantly higher survival rate, p <0.001.

A second method to adjust for differences in baseline risk between the 2 groups of patients was to use the Cox proportional-hazards model. The results of these analy-

TABLE II Percentage of Patients Who Have a Given Finding					
Finding	PTCA (n = 632)	Bypass Surgery (n = 1730)	Relative Odds*	Chi-Square Value	p Value
General					
High risk†	12.0	24.9	2.4	45.3	<0.001
Female gender	38.0	28.7	0.8	18.7	<0.001‡
Age > 70 years	35.1	40.4	1.2	5.4	0.020
Cardiac					
Cardiac impairment	9.0	12.3	1.4	4.8	0.028
CHF on chest x-ray	2.5	6.8	2.7	15.9	<0.001‡
S_3 gallop	0.6	3.1	4.8	11.6	0.001‡
History of CHF	4.4	6.3	1.4	3.0	0.085
CAD in 1 vessel§	44.2	7.6	0.1	286.4	<0.001
CAD in 2 vessels§	36.3	23.8	0.5	25.1	<0.001
CAD in 3 or 4 vessels§	19.5	68.7	9.0	309.1	<0.001
Atrial fibrillation	2.4	2.2	0.9	0.1	0.797
Ventricular premature complexes	5.2	6.5	1.3	1.4	0.242
Murmur	5.2	5.0	1.0	0.1	.805
History of MI	24.5	36.2	1.5	28.4	<0.001‡
Pulse > 109	1.7	2.4	1.4	0.9	0.356
Ventricular aneurysm	0.0	2.3	---	14.9	<0.001
MI age undetermined	11.7	18.4	1.6	14.9	<0.001
History of CABG	14.7	9.7	0.7	11.8	0.001‡
History of PTCA	11.2	2.2	0.2	85.9	<0.001‡
Graft failure	0.5	1.3	2.8	3.1	0.078‡
Cardiopulmonary					
Respirations ≥ 20	21.4	22.6	1.1	0.4	0.521
Wheezing	4.4	4.9	1.1	0.2	0.626
History of COPD	5.9	6.2	1.1	0.1	0.728
History of cigarette smoking	3.2	3.4	1.1	0.1	0.821
History of SOB	6.6	6.8	1.0	0.0	0.920
Infiltrate	1.7	2.4	1.4	1.0	0.318
PO2 <75	4.9	11.5	2.3	22.9	<.001
Metabolic					
Renal impairment	6.8	8.9	1.3	2.7	0.103
Sodium <130 mEq/liter	1.6	1.9	1.2	0.3	0.601
Diabetes mellitus	19.0	26.1	1.4	12.7	<0.001‡
pH > 7.45	0.9	7.5	7.9	36.8	<0.001‡
pH <7.35	0.5	1.8	3.8	5.7	0.017‡
Other					
Banks > 10%	2.1	2.3	1.1	0.1	0.711
Temperature > 38.3°C	0.5	1.5	3.2	4.0	0.045
Hematocrit <30	2.1	4.9	2.4	9.2	0.002
History of stroke/TIA	3.8	6.0	1.6	4.2	0.040

*Relative odds for CABG patients to have the finding compared with PTCA patients. Values <1 indicate that CABG patients were less likely to have the finding than PTCA patients.
†Having a MedisGroups admission severity group score of 2 to 4.
‡Significant in multiple logistic analysis for predicting revascularization procedure.
§Based on 446 PTCA patients and 1,098 bypass surgery patients with a catheterization report in the hospital record.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PO2 = oxygen partial pressure; PTCA = percutaneous transluminal coronary angioplasty; SOB = shortness of breath; TIA = transient ischemic attack.

ses are presented in Table III for all patients combined and for patients divided into 2 risk groups on the basis of the MedisGroups severity score. There were 13 findings that were significantly associated with mortality for all patients combined. Because the high- and low-risk groups are smaller and more homogeneous, there were fewer significant risk factors in each of the severity groups than overall. Three of the risk factors for the low-risk patient were not direct measurements of physiologic status: age, previous CABG and number of diseased vessels. The risk factors for the high-risk group of patients were cardiac, renal or pulmonary impairment. All of these risk factors may have a cardiac basis.

The Cox model, as previously defined, was used to compare the mortality risk for the 2 revascularization procedures according to risk group and during 3 time intervals (the entire course of the study, the first 60 days and after 60 days). The results of these analyses are presented in Table IV. CABG patients had a higher mortality than PTCA patients after adjusting for the covariates. The relative risk, R, of mortality for CABG compared with PTCA patients was 1.72 (p = 0.001). The relative risk was much higher for the low-risk patients (R = 2.15, p = 0.0003), primarily because of the high relative risk for CABG during the first 60 days (R = 3.8, p = 0.0004). There was no significant difference in the mortality rates for the high-risk patients. However, the mortality rate for the CABG patients was lower than for the PTCA patients, because the CABG patients had a lower long-term mortality (R = 0.67, p = 0.26). The relatively better results for the PTCA patients among the low-risk than the high-risk patients was statistically significant (p = 0.01 for interaction).
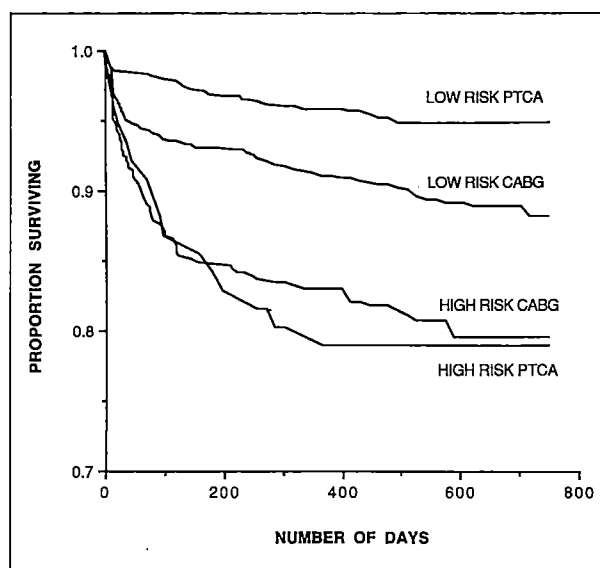
FIGURE 2. Survival curves for high- and low-risk patients who had percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG).

TABLE III List of Regression Coefficients, Relative Risks and 95% Confidence Intervals for All Variables Significant in a Cox Proportional-Hazards Regression

Finding	Regression Coefficient	Relative Risk	95% Confidence Interval Lower Bound	Upper Bound
All Patients (n = 2,362)				
Age >80 years	1.133§	3.10	1.77	5.45
Fever	0.939‡	2.56	1.30	5.03
History of CHF	0.867§	2.38	1.68	3.38
Renal impairment	0.848§	2.33	1.71	3.19
Bands >10%	0.701	2.02	1.12	3.63
Cardiac impairment	0.678§	1.97	1.46	2.67
Wheezing	0.658‡	1.93	1.27	2.92
Atrial fibrillation	0.641	1.90	1.06	3.40
Ventricular aneurysm	0.640	1.90	1.02	3.52
History of CABG	0.423	1.53	1.09	2.14
Diabetes mellitus	0.366‡	1.44	1.11	1.88
Low-Risk Patients* (n = 1,856)				
Ventricular aneurysm	1.353‡	3.87	1.57	9.52
Age >80 years	1.107	3.03	1.59	5.77
Age >70 years	0.361	1.44	1.03	1.99
Atrial fibrillation	1.039	2.83	1.43	5.57
History of COPD	0.684	1.98	1.14	3.44
History of CABG	0.612	1.84	1.20	2.82
High-Risk Patients† (n = 506)				
History of CHF	1.167§	3.21	2.03	5.09
Renal impairment	1.133§	3.10	2.07	4.66
Cardiac impairment	0.892§	2.44	1.64	3.64
Wheezing	0.613	1.85	1.12	3.05

*Low risk is defined as admission severity group score 0 or 1.
†High risk is admission severity group score 2 to 4.
‡p <0.01; §p <0.0001.
Abbreviations as in Table II.

TABLE IV Relative Risk of Mortality for CABG Patients Compared with PTCA Patients After Adjusting for Initial Clinical Status

Time Interval	All Patients (n = 2,362)			Low-Risk Patients* (n = 1,856)			High-Risk Patients† (n = 506)		
	Dead (n)	R	p Value	Dead (n)	R	p Value	Dead (n)	R	p Value
Entire study	260	1.72	0.001	161	2.15	0.0003	99	0.90	0.69
0 to 60 days	128	2.75	0.0004	80	3.79	0.0004	48	1.26	0.60
After 60 days	132	1.22	0.35	81	1.50	0.13	51	0.67	0.26

*Admission severity group score 0 or 1.
†Admission severity group score 2 to 4.
R = relative risk; other abbreviations as in Table II.

One important omitted risk factor that is likely to be much more prevalent in the CABG than PTCA patients is left main coronary artery stenosis. To estimate the effect of the left main disease on the mortality rate, we used the data from elderly patients in the Coronary Artery Surgery Study. For that study the percentage of subjects with left main disease was 13% and the relative risk of perioperative mortality for these subjects was 2.6. Making the conservative assumption that no PTCA patients had left main disease and that left main disease was unrelated to any of the patient characteristics measured in this study, the presence of left main disease alone would account for a relative risk of (0.13) (2.6) + (0.87) (1.00) = 1.2. Thus the higher percentage of left main disease in the CABG patients probably contributes to the higher mortality rates for the CABG patients, but it does not account for a relative risk as large as the 2.15 found for the low-risk CABG patients. On the other hand, it is possible that the relative risk of 0.90 for CABG among the high-risk patients would be lower and statistically significant after adjusting for left main disease.

DISCUSSION

There were 4 principal findings from this study:

1. For the PTCA patients the postprocedure mortality rate and the rate of CABG during the same stay were higher in this study than that reported for PTCA patients treated at academic centers. In 1985, there may have been substantial differences between efficacy (technology performance in an ideal setting) and effectiveness (performance in the overall population). In contrast, the mortality risk of patients undergoing CABG was similar to that reported nationally.

2. CABG patients were at higher mortality risk before the procedure than PTCA patients. This suggests that the procedures were not considered as equivalent alternatives.

3. After adjusting for initial patient risk, CABG patients had a higher risk of mortality during the perioperative and recovery period. Some portion of the difference may be related to the presence of left main disease that was not recorded in this study.

4. The relative risk of CABG compared with PTCA was affected by the initial patient risk at the time of the procedure. For low-risk patients the mortality rates were significantly lower with PTCA. For high-risk patients the mortality rates were lower for CABG, but the difference was not statistically significant.

The relation between initial patient risk and the efficacy of surgery is plausible. Low-risk patients should have good survival regardless of treatment, and the complications of CABG will account for a high percentage of the mortality of low-risk patients. However, high-risk patients, particularly those with a low ejection fraction, benefit more from CABG than other patients,[2,11,14] and after the perioperative and recovery periods, it is possible that CABG patients would survive better in the long term than PTCA patients. Although information on ejection fraction was not available in this study, a high Medisgroup severity score in our data set may result from patient findings that are a consequence of impaired left ventricular function, e.g., congestive heart failure, impairment of renal or pulmonary function. Our data are inadequate, however, to determine whether a particular finding is secondary to cardiac function.

It is important that the results of this study be placed in an appropriate methodologic perspective. More definitive comparisons of the efficacy of the 2 procedures must await the results of clinical trials.[16] The trial results alone, however, will be insufficient for guiding treatment decisions because the trials are usually conducted in selected centers and in highly selected patients. The Coronary Artery Surgery Study, e.g., excluded from randomization for various reasons >90% of patients undergoing catheterization for suspected coronary artery disease recorded in the Coronary Artery Surgery Study registry.[17] Although the data from the present study have limitations, they also have advantages over many observational data sets: (1) They come from community hospitals in several areas of the country. (2) There is extensive clinical information available on each patient. (3) They were collected in the same manner for PTCA and CABG patients. Therefore the results of this study should be a good estimate of the effectiveness of the procedures as performed generally.

The efficacy of PTCA in published reports appears to differ from the effectiveness observed in this series. The in-hospital mortality rate after PTCA has been reported to be from 0.1 to 1.2%, and the rate of CABG after PTCA has been reported to be from 1.8 to 7.0%.[18-25] Although higher rates have been reported in an earlier review of the literature,[26] in general both the mortality rate and the CABG rate in this study appear

to be higher than in others. Our results suggest that the patients, the providers, or both differ between reporting academic centers and representative providers. Diffusion of the technology from academic centers into the community may still have been occurring in 1986.

In contrast, the 30-day mortality rate for CABG patients of 6.4% among all Medicare patients in the USA was similar to the perioperative mortality rates of 5.2[12] and 7%[27] presented in the literature for elderly patients. This suggests that the patients and providers in the literature for CABG are more representative of the national experience than the patients and providers for angioplasty.

We recognize that the results from this study are not definitive. Patients were not randomized to treatment, the types of patients clearly differ between the 2 procedures, and efforts at risk adjustment were compromised by imperfect information on risk factors. However, there is substantial clinical information in this data base, and the random selection of patients on a national scale has advantages over many studies of technology assessment. The results from this study suggest some potential advantages and disadvantages of using routinely available information on large representative populations and highlight the complementary nature of research from multiple sources.

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Cardiac Response to Combined Moderate Heat and Exercise in Men with Coronary Artery Disease

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The effect of moderate heat stress on cardiac performance during sustained moderate physical work was evaluated in men ≥6 weeks after a cardiac event. Subjects (n = 10) performed upright leg cycle ergometer exercise at approximately 50% of peak oxygen uptake for up to 60 minutes in warm (30.0 ± 0.9°C) and thermoneutral (21.5 ± 0.3°C) environments. Cardiac output (carbon dioxide rebreathing method), left ventricular ejection fraction and relative left ventricular end-diastolic volume (portable nuclear VEST monitor) were periodically determined. In both environments, heart rate increased (p <0.05), stroke volume decreased (p <0.05), and cardiac output remained unchanged with exercise time. In the warmer environment, heart rate was increased (p <0.05) and stroke volume tended to be decreased (p <0.08), with no difference in cardiac output. In both environments, left ventricular ejection fraction did not change from minute 6 to 60 of exercise, whereas relative left ventricular end-diastolic volume decreased (p <0.05) with exercise time. Arterial blood pressure was unchanged from minute 6 to 60 in the warm environment. Arrhythmias were not altered by exercise time or environment, and no subjects had evidence of myocardial ischemia. The data indicate that although heart rate increased and stroke volume and relative left ventricular end-diastolic volume decreased with exercise time, cardiac output and left ventricular ejection fraction remained unchanged in both thermoneutral and warm environments. The results suggest that there is preserved cardiac function in men with uncomplicated coronary artery disease when performing sustained moderate work in combination with moderate heat stress.

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Heat stress can increase the demands on the cardiovascular system during exercise owing to increased thermoregulatory blood flow requirements. The effect of heat stress on cardiac function depends on exercise intensity and duration, magnitude of heat stress, hydration level, acclimation state and exercise capacity.[1-3] Little is known regarding the effect of heat stress on cardiac function during exercise in subjects with coronary artery disease. Reduced cardiac reserve and maximal oxygen uptake in these subjects could limit the ability to achieve combined thermoregulatory and metabolic blood flow demands.[4] Fluid and electrolyte reductions together with a possible augmented sympathetic nervous activation state[1-3,5,6] could also increase the incidence of arrhythmias. The present study evaluates the influence of heat stress on cardiac function during sustained moderate exercise in men with known coronary artery disease. A moderate rather than a high heat load was selected to promote safety and still provide information on work conditions more likely to be encountered by cardiac patients with occupational, home or leisure activities.

METHODS
Subjects: Ten asymptomatic men (average age 60 ± 2 years, average weight 86.0 ± 5.4 kg) who had a myocardial infarction (8 inferior and 1 non-Q-wave), coronary artery bypass surgery (n = 4) or percutaneous angioplasty (n = 1), or a combination, ≥6 weeks before the study were examined. All subjects were at low to moderate risk. Medications included β-blockers (n = 3), calcium antagonists (n = 3), digitalis (n = 1), diuretics (n = 1) and nitrates (n = 1). All subjects were participating in an exercise program. The study was conducted from July through September 1990. Subjects agreed to the protocol approved by the Institutional Human Research Review Committee.

Preliminary session: All subjects initially performed a treadmill exercise test using a modified Balke protocol.[7] Any subject unable to exercise to fatigue or achieve ≥5 METs was excluded. A 12-lead electrocardiogram was periodically recorded. Oxygen uptake was measured by open-circuit spirometry.

Experimental session: At least 3 days after the treadmill exercise test, subjects reported for placement of an ambulatory ventricular function monitor (VEST, Capintec, Inc.). The VEST radiation detector was centered over the left ventricular blood pool with the aid of a gamma scintillation camera. A second detector was placed over the right lung to monitor background radionuclide activity. Before placement of the VEST, red

blood cells were labeled in vivo with 25 to 30 mCi of technetium-99m, and left ventricular ejection fraction was determined at rest (seated position) in the left anterior oblique view using multigated acquisition imaging procedures. A red marker was placed at the top edge of the VEST garment on the subject's chest to enable evaluation of possible movement of the garment during the experimental sessions.

Baseline VEST measurements were obtained with the subject in the seated posture. The subject then underwent 2 leg cycle ergometer tests separated by approximately 3 hours; 1 study was performed in a thermoneutral (21.5 ± 0.3°C) laboratory and the other outdoors in a warm (30.0 ± 0.9°C) environment. Humidity averaged 53 ± 1% indoors and 47 ± 2% outdoors. The order of testing was rotated so that the same number of subjects was tested first in each environment. The subject wore shorts and a T-shirt.

The procedures for the exercise tests in the 2 environments were the same. The subject sat on a leg cycle ergometer for 10 minutes and then exercised for up to 60 minutes at a work load estimated to need approximately 50% of peak oxygen uptake. Work load (W) was the same in both environments. Measurements obtained at rest and during exercise at minutes 6, 20, 40 and 60 included oxygen uptake by open-circuit spirometry (meteorologic balloon used to collect expired air), heart rate by telemetry, cardiac output by the carbon dioxide rebreathing procedure,[8] rating of perceived effort according to the Borg 6- to 20-point scale,[9] and blood pressure by mercury sphygmomanometer. The electrocardiogram was monitored for 9 minutes after exercise. Sweat was wiped off the subject's face and extremities, and body weight was reassessed before drinking water. The change in weight with each exercise session was used to estimate sweat loss, although sweat loss from the trunk region was not accounted for because the clothing (T-shirt and shorts) underneath the VEST garment was not removed. Between the 2 tests, the subject rested in the upright position. Fluid intake was encouraged, and the subject was instructed to eat lunch ≥2 hours before the second test. At the end of the second test, the subject returned to the nuclear testing laboratory. The positioning of the VEST detector mount was checked visually, as well as with the gamma scintillation camera.

VEST data analysis: The VEST-recorded tape was analyzed at 30-second intervals for left ventricular ejection fraction and relative left ventricular end-diastolic and end-systolic volumes by an independent, experienced technician. In the determination of relative left ventricular volumes, end-diastolic volume at the beginning of the tape in the seated position in the nuclear laboratory was designated as 100%, and all other end-diastolic and end-systolic volumes were calculated relative to this volume. Incidence of arrhythmias and electrocardiographic ST-segment changes were also evaluated from the VEST tape. Before each tape was analyzed, the technical adequacy of the data was assessed in a 3-step process as follows: (1) comparison of static gamma camera images obtained before and after completion of the study to assess possible changes in VEST

TABLE I Initial Adjustments to Exercise

Parameter	Environment	Rest	Exercise (min 6)
Heart rate	Thermoneutral	73 ± 3	92 ± 3*
(beats/min)	Warm	74 ± 3	95 ± 2*
Stroke volume	Thermoneutral	58 ± 4	91 ± 10*
(ml/beat)	Warm	50 ± 4	84 ± 6*
LV ejection fraction	Thermoneutral	45 ± 5	49 ± 5
(%)	Warm	45 ± 4	53 ± 5*
LV end-diastolic	Thermoneutral	88 ± 5	99 ± 4*
volume (%)	Warm	79 ± 4	90 ± 4*
LV end-systolic	Thermoneutral	48 ± 7	50 ± 7
volume (%)	Warm	43 ± 3	41 ± 3
Systolic pressure	Thermoneutral	138 ± 7	175 ± 1*
(mm Hg)	Warm	135 ± 9	165 ± 9*

*$p < 0.05$ versus rest.
Values are mean ± SE (n = 10).
LV = left ventricular.

detector positioning, (2) evaluation of trend plots of left ventricular and background counts over time for any abrupt change suggestive of detector movement, and (3) evaluation of individual time-activity curves. Other studies[10-16] showed that left ventricular ejection fraction data obtained from the VEST at rest or with dynamic exercise, or both, is accurate compared with gamma camera data, and is highly reproducible and consistent with known responses in cardiac patients.

Statistical analysis: Analysis of variance with repeated measures was used to evaluate the effect of exercise time (6 to 60 minutes) within each environment and that of environmental temperature (thermoneutral and warm) at minutes 20 through 60. In evaluating the latter effect, 3 subjects prescribed β blockers were excluded owing to different elapsed periods of time between receiving this medication and the beginning of the exercise session in the 2 environments. This was done because the depressive effect on heart rate (and presumably other parameters of cardiac function) could vary with time after ingestion of β blockers.[17] Differences between means were assessed with Fisher's protected least significant difference test. Paired t tests were used to compare responses from rest to minute 6 of exercise in each environment and between rest data in the 2 environments. Significance levels were tested at the 0.05 level. All values are reported as mean ± SE.

RESULTS

Preliminary treadmill test: Peak oxygen uptake, heart rate, systolic pressure, respiratory exchange ratio and rating of perceived effort in the 10 subjects averaged 25.6 ± 0.9 ml/kg/min, 140 ± 6 beats/min, 199 ± 9 mm Hg, 1.14 ± 0.03 and 18 ± 0, respectively. Peak METs ranged from 5.8 to 8.6. No subject had an ischemic response based on electrocardiographic ST-segment analysis or symptoms.

Initial adjustments to exercise in two environments: Table I lists responses at rest and at minute 6 of exercise. No significant differences existed between the 2 environments at rest. Heart rate, stroke volume, cardiac output, end-diastolic volume and systolic pressure increased ($p < 0.05$) with exercise at minute 6 in both environments, and end-systolic volume decreased (p

<0.05) with the onset of exercise. Left ventricular ejection fraction increased (p <0.05) at minute 6 in the warm environment, but the increase did not attain significance by minute 6 in the thermoneutral condition.

Tolerance to moderate exercise in heat stress: One subject stopped the exercise test at 40 minutes in the warm environment and indicated before the test in the thermoneutral environment that he did not want to exercise >40 minutes. All other subjects completed 60 minutes of exercise in the 2 environments. Oxygen uptake during exercise at minutes 6, 20, 40 and 60 averaged 12.2 ± 0.7, 12.8 ± 0.8, 12.9 ± 0.6 and 12.7 ± 0.7 ml/kg/min, respectively, in the thermoneutral environment, and 12.3 ± 0.8, 12.9 ± 0.7, 13.0 ± 0.5 and 12.8 ± 0.8 ml/kg/min, respectively, in the warm environment. No differences were observed in oxygen uptake with exercise time or environment. Rating of perceived effort increased (p <0.05) progressively with exercise time in both environments, but did not differ between the 2 environments. The ratings determined at 6, 20, 40 and 60 minutes averaged 10 ± 1, 11 ± 1, 12 ± 1 and 13 ± 1, respectively, in the thermoneutral condition, and 9 ± 1, 11 ± 1, 12 ± 1 and 13 ± 1, respectively, with heat stress.
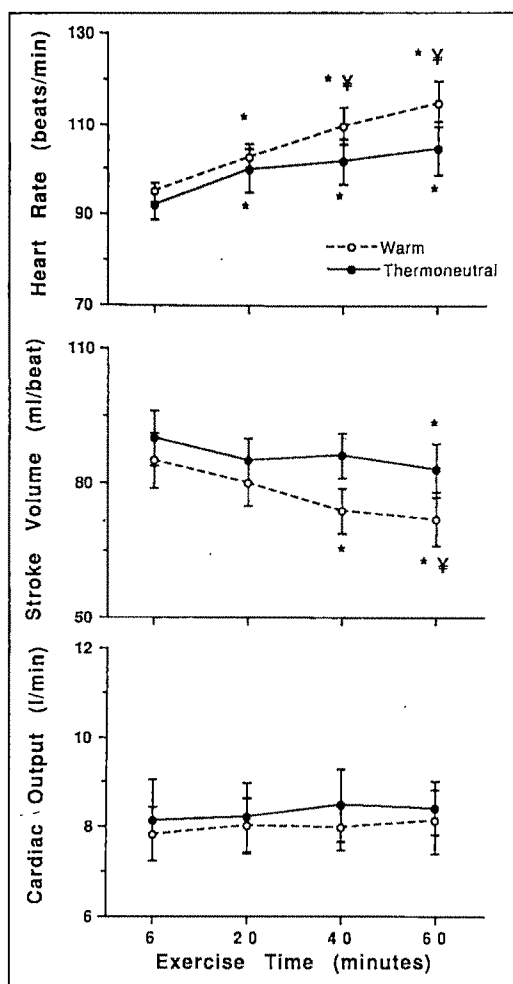
FIGURE 1. Heart rate, stroke volume and cardiac output during 60 minutes of exercise in warm and thermoneutral environments (n = 10). *p <0.05 vs minute 6; ¥ p <0.05 vs minute 20.

Cardiac response to exercise in heat stress: Heart rate, stroke volume and cardiac output during exercise in the 2 environments are shown in Figure 1 (all subjects) and Table II (subjects not prescribed β blockers). With exercise time in both environments, heart rate increased (p <0.05), stroke volume decreased (p <0.05), and cardiac output did not change. Heart rate was increased (p <0.05) at minute 20 compared with minute 6 in both environments. In the warm environment, a further increase (p <0.05) was observed at minute 40 compared with minute 20. At minutes 40 and 60, heart rate was higher (p <0.05) in the warm than in the thermoneutral environment (Table II).

Exercise stroke volume decreased (p <0.05) at minute 40 compared with minute 6, as well as at minute 60 compared with minute 20 in the warm environment (Figure 1). In the thermoneutral condition, stroke volume was decreased (p <0.05) at minute 60 compared with minute 6. Between the 2 environments, stroke volume tended (p <0.08) to be lower with heat stress than in the thermoneutral environment. Cardiac output did not differ between environments.

Left ventricular ejection fraction and relative end-diastolic and end-systolic volumes are shown in Figure 2 and Table II. Ejection fraction did not change during exercise from minute 6 to 60 in each environment. In comparing the response between the 2 environments, left ventricular ejection fractions were similar (Table II).

Relative left ventricular end-diastolic volumes decreased (p <0.05) with exercise time in both environments (Figure 2). The initial decrease occurred at minutes 20 and 40 in the warm and thermoneutral environments, respectively. A further decrease (p <0.05) was observed from minute 20 to 60 in the thermoneutral condition. Relative end-diastolic volume tended to be decreased (p <0.06) in the warm environment (Table II).

Left ventricular end-systolic volume decreased (p <0.05) at minute 20 with exercise time in the thermoneutral condition, with no further significant change with exercise up to 60 minutes (Figure 2). In the warm environment, no significant change was observed from minute 6 through 60. Relative left ventricular end-systolic volumes tended to be decreased (p <0.09) in the warm environment (Table II).

Systolic pressure determined at minutes 6, 20, 40 and 60 of exercise, averaged 178 ± 12, 174 ± 10, 175 ± 11 and 169 ± 11 mm Hg, respectively, in the thermoneutral condition, and 168 ± 9, 159 ± 11, 168 ± 13 and 164 ± 12 mm Hg, respectively, in the warm environment. The only changes (p <0.05) observed with work time were between minutes 60 and 6 in the thermoneutral environment and between minutes 20 and 6 with heat stress. Systolic pressure was decreased (p <0.05) only at minute 20 in the warm environment compared with in thermoneutral conditions.

Diastolic pressure during exercise at minutes 6, 20, 40 and 60 averaged 86 ± 4, 83 ± 4, 84 ± 4 and 82 ± 4 mm Hg, respectively, in the thermoneutral environment, and 82 ± 4, 79 ± 3, 80 ± 3 and 77 ± 2 mm Hg, respectively, in the warm condition. In both conditions,

Parameter	Environment	Exercise				p Value
		Minute 6	Minute 20	Minute 40	Minute 60	
Heart rate (beats/min)	Thermoneutral	94 ± 3	103 ± 4	106 ± 5	112 ± 5	
	Warm	96 ± 3	106 ± 4	115 ± 4*	120 ± 5*	0.01
Stroke volume (ml/beat)	Thermoneutral	89 ± 14	80 ± 12	82 ± 10	78 ± 8	
	Warm	81 ± 9	79 ± 7	71 ± 7	69 ± 8	0.08
LV ejection fraction (%)	Thermoneutral	50 ± 4	52 ± 4	50 ± 3	52 ± 4	
	Warm	50 ± 7	52 ± 6	50 ± 6	53 ± 6	0.21
LV end-diastolic volume (%)	Thermoneutral	100 ± 4	97 ± 5	96 ± 4	94 ± 4	
	Warm	89 ± 4	86 ± 4	84 ± 3	83 ± 2	0.06
LV end-systolic volume (%)	Thermoneutral	54 ± 8	50 ± 9	50 ± 8	47 ± 7	
	Warm	43 ± 4	40 ± 5	41 ± 4	39 ± 4	0.08
Systolic pressure (mm Hg)	Thermoneutral	181 ± 14	176 ± 13	179 ± 15	172 ± 14	
	Warm	170 ± 12	163 ± 13*	172 ± 16	167 ± 14	0.04
Diastolic pressure (mm Hg)	Thermoneutral	86 ± 5	82 ± 5	84 ± 6	82 ± 5	
	Warm	81 ± 5	81 ± 4	81 ± 4	77 ± 3	0.19

*p <0.05 versus thermoneutral.
Values are mean ± SE (n = 7).
LV = left ventricular.

diastolic pressure was decreased (p <0.05) at 60 minutes compared with 6 minutes. Between environments, no significant difference was observed for diastolic pressure.

No subject had frequent or complex ventricular arrhythmias during exercise in either environment. Occasional (3 to 6/min) ventricular arrhythmias were observed in 2 subjects in the thermoneutral and 1 in the heat exercise periods. Except for 1 subject who had frequent arrhythmias during minute 7 of recovery in the thermoneutral environment, arrhythmia rate was not increased in the immediate recovery period. No subject reported anginal symptoms or had electrocardiographic evidence of myocardial ischemia. Body weight reduction averaged 0.4 kg in the thermoneutral environment (n = 6) and 0.5 kg in the warm environment (n = 7).

DISCUSSION

Subjects with coronary artery disease had an increase in heart rate, a decrease in stroke volume, and maintenance of cardiac output during sustained moderate exercise combined with moderate heat stress. These directional responses as well as the magnitude of changes are consistent with those reported in normal subjects under similar temperature and exercise conditions.[18,19]

Most evidence indicates that the increase in heart rate with sustained moderate work in both thermoneutral and warm conditions is a compensatory response to maintain cardiac output with a decreasing stroke volume; the latter is generally attributed to decreased cardiac preload associated with increased cutaneous blood volume, vascular fluid filtration and body water reduction.[1-3] Central blood volume and venous pressure have been shown to decrease during exercise in normal subjects with exposure to heat stress,[1-3,20] although the effect on left ventricular volume during exercise has not (to our knowledge) been evaluated. In the present study, men with coronary artery disease demonstrated a significant reduction in relative left ventricular end-diastolic
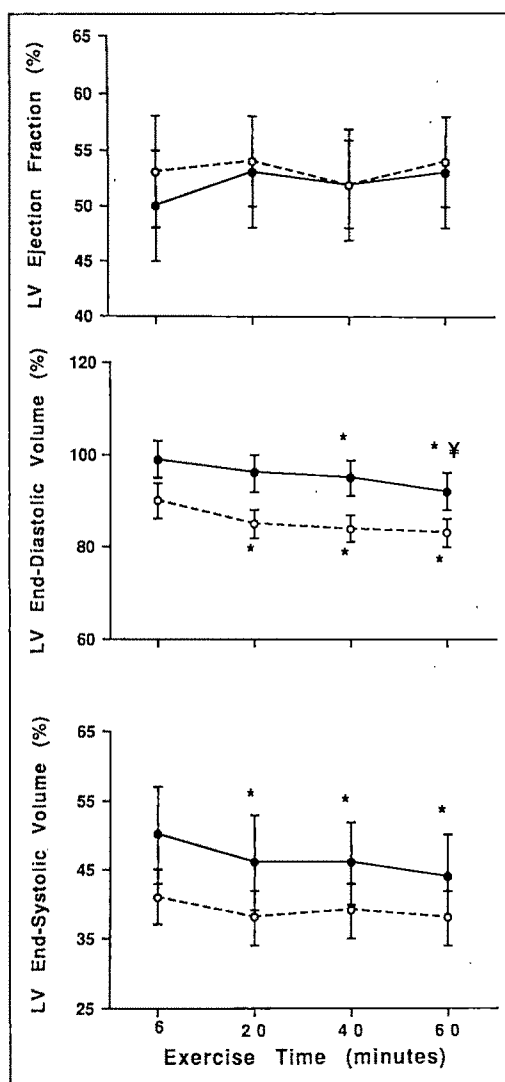
FIGURE 2. Left ventricular (LV) ejection fraction and relative end-diastolic and end-systolic volumes during 60 minutes of exercise in warm and thermoneutral environments (n = 10). *p <0.05 vs minute 6; ¥ p <0.05 vs minute 20.

volume in both the warm and thermoneutral environments.

Although less accepted, another hypothesis postulated to account for the decrease in stroke volume with exercise time in a warm environment is reduced myocardial function.[1,3] Based on left ventricular ejection fraction, myocardial function did not appear to deteriorate with exercise time in men with coronary artery disease. Mean ejection fraction remained unchanged from minute 6 to 60 in the warm environment, and no subject (even those [n = 3] with a resting left ventricular ejection fraction <40%) had a decrease in ejection fraction less than resting levels at minute 60 of exercise in the warm environment (Figure 3). Thus, despite significant alterations in stroke volume, heart rate and left ventricular end-diastolic volumes with exercise time, ejection fraction was preserved during moderate exercise combined with moderate heat stress. Compared with at rest, mean ejection fraction increased ≥8% at minute 20 in both environments. This magnitude of increase is generally considered a normal response and suggests the absence of ischemia. The unchanged systolic pressure at minute 60 compared with minute 6 in the warm environment further indicates that the cardiac output response was adequate to maintain peripheral perfusion pressure.

It is possible that heat stress could increase arrhythmogenesis through electrolyte changes, or increased myocardial oxygen requirements or sympathetic nervous activation, or a combination. Subjects in the present study did not have a greater incidence of arrhythmias with work time or heat stress. Although decreased venous return and increased circulating catecholamines in the immediate recovery period could theoretically provoke an increase in the incidence of arrhythmias in the warm environment, this was not observed.

Study limitations: One limitation of the study was that core temperature was not measured. In normal subjects, other studies showed that core temperature during 1 hour of moderate exercise is independent of air temperature between the range of 5 and 30°C.[21,22] The mean temperature in the warm environment was 30°C, suggesting that the increase in core temperature probably did not differ substantially between the 2 environments. Further support for an appropriate core temperature was the ability of subjects to maintain systolic pressure from 6 to 60 minutes. Rowell[2] reported that mean arterial pressure decreased when core temperature was >39°C.

The 2 exercise sessions were scheduled on the same day owing to the use of a radioisotope. Thus, patients were tested at a different time of day in the 2 environments. An equal number were tested first in each environment, and subjects prescribed β blockers were excluded from the statistical analysis of the environmental factor owing to the drug's potential variable impact on heart rate and other indexes of cardiac function in relation to the elapsed time between receiving the medication and performing exercise. With regard to application to the occupational setting, the work intensity selected only slightly exceeded the average 8-hour intensity level (i.e., 40% of peak oxygen uptake) frequently cited as appropriate.[23] Thus, the conditions of this study (in which subjects performed 1 hour of work at 50% of peak oxygen uptake in the morning and 1 hour in the afternoon) are within this guideline and could be found in the occupational work setting.

Clinical implications: The maintenance of cardiac output, left ventricular ejection fraction and systolic pressure during sustained work in the warm environment suggests that cardiac function did not deteriorate during sustained moderate exercise combined with moderate heat stress in stable patients with coronary artery disease who have relatively good functional exercise tolerance.

The progressive increase in heart rate over exercise time suggests that clinicians may advise patients to use heart rate to assess the magnitude of cardiovascular drift occurring during sustained work with heat stress. Although it appears logical to predict that an upright drift in heart rate would increase myocardial oxygen requirements, the effect of this drift on myocardial ischemic thresholds remains unknown. A decrease in left ventricular end-diastolic volume with exercise time, together with some tendency for systolic pressure to be decreased in the warm environment, may decrease left
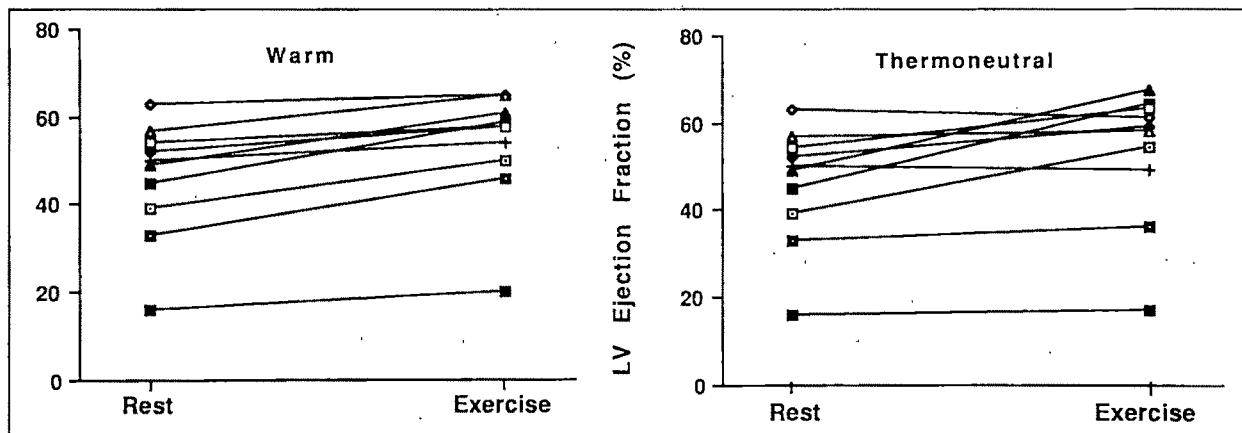
FIGURE 3. Individual left ventricular (LV) ejection fraction responses at rest and end of exercise in thermoneutral and warm environments.

ventricular wall tension or afterload, or both, and thereby offset some of the increase in myocardial oxygen requirements expected from the increased heart rate.

Perceived effort increased over time, indicating that it may be used by workers to adjust work rates during sustained work. However, rating of perceived effort did not reflect the differences between the warm and thermoneutral environments, suggesting that heart rate provides a more sensitive marker of increased thermoregulatory cardiovascular demands.

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Mechanisms and Dynamics of Episodes of Progression of 2:1 Atrioventricular Block in Patients with Documented Two-Level Conduction Disturbances

Agustin Castellanos, MD, Marilyn M. Cox, MD, Pedro R. Fernandez, MD,
Alberto Interian, Jr., MD, Manuel Mayor, MD, Tomas Ravina, MD,
and Robert J. Myerburg, MD

Twenty episodes of progression of 2:1 atrioventricular (AV) block were identified during incremental atrial stimulation in 7 patients with documented (2-level) block in the AV node and His-Purkinje system. All occurred at cycle lengths shorter than those at which stable 2:1 HV block had been detected. Thirteen episodes were typical since 2:1 increased to 3:1 AV block when an atrio-His (AH) Wenckebach period was completed with an atrial impulse that otherwise would have been conducted. These episodes occurred with dynamic A(M): V(N) ratios similar to those seen at the AV node. Seven atypical episodes were identified (while AH Wenckebach periods were occurring): (1) 2:1 increasing to 3:1 AV block and then to 4:1 AV block resulting from prolonged refractoriness in the His-Purkinje system subsequently followed by concealed conduction in the latter structure; (2) conversion of 3:2 directly into 3:1 AV block due to block of the next-to-last atrial impulse in the His-Purkinje system with completion of AH Wenckebach period with the following atrial impulse; and (3) 4:2 AV block presumably due to supernormal conduction in a transversely dissociated His-Purkinje system. These episodes occurred with A(M): V(N) ratios, which in other structures would have been indicative of different degrees of AV block. In conclusion, progression of 2:1 AV block during documented 2 level conduction disturbances (1) can be explained by mechanisms different than those currently known, and (2) has rich, but different dynamics from those observed exclusively in the AV node and exclusively in the His-Purkinje system.

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Several mechanisms have been proposed to explain pacing-induced increases of 2:1 atrioventricular (AV) block into higher degrees of block resulting from conduction disturbances occurring exclusively in the AV node, exclusively in the His-Purkinje system or, simultaneously, in both structures.[1-12] In addition, recently, some clinical and experimental studies dealt with the dynamics of complex AV conduction, or phase-locked stimulus response, patterns produced by rapid electrical stimulation.[13-17] However, as far as we know, few publications have discussed previously undescribed mechanisms and the dynamics of pacing-induced progression of 2:1 AV block in which there are documented 2-level conduction disturbances in 2 separate structures, as will be done in this communication.

METHODS

Study patients: Seven consecutive patients in whom HV and, consequently, AV block developed during electrophysiologic evaluation constitute the basis of this study. In 6 patients the conduction disturbance appeared while pacing the atria, and in 1 during sinus rhythm.

Electrophysiologic study procedure: After informed consent was obtained in accordance with the guidelines of our institution, electrophysiologic studies were performed in the postabsortive state.[18] All antiarrhythmic medications were discontinued for ≥2 days. Although complete electrophysiologic evaluation was performed, this study deals only with the results of incremental atrial pacing using twice-diastolic threshold stimuli.

In all cases, 2:1 HV (and AV) block was seen during incremental atrial stimulation at HH intervals that were equal to the corresponding stimulus-stimulus and atrial(A)-A intervals. Once this had occurred, pacing was continued in decrements of 10 to 20 ms until ≥3:1 degrees of AV block appeared. The latter invariably resulted from coexisting 2-level block in 2 separate structures, namely, AV node and His-Purkinje system. Episodes of progression of 2:1 AV block were classified for didactic reasons, as typical or atypical, according to whether they conformed to previously held views regarding pacing-induced 2-level block in 2 separate structures or to the dynamics of progression of human AV nodal or His-Purkinje block.[1-15]

TABLE I Clinical and Electrophysiologic Information

Pt. No.	Age (yr) & Sex	Diagnosis	QRS Complexes	AH	HV	HH of 2:1 HV	Episodes	A(M):V(N) Ratios
1	42F	SVT	RBBB	115	45	360	T:3	7:3; 9:4; 11:5
							A:1	6:3
2	69M	SVT	N	110	50	390	T:4	9:4; 9:4; 9:4
								11:5
3	67M	PAVB	RBBB	120	45	510	T:2	7:3; 9:4
4	71F	PAVB	RBBB	120	55	625	T:3	7:3; 9:4; 9:4
5	63M	PAVB	RBBB	115	55	·470	T:1	9:4
6	62F	PAVB	RBBB	135	50	790*	A:3	9:3; 9:3; 9:3
7	42F	Syncope	N	120	55	400	A:3	4:2; 4:2; 4:2

*During sinus rhythm.
A = atypical; N = narrow; PAVB = paroxysmal atrioventricular block; RBBB = right bundle branch block; SVT = supraventricular tachycardia; T = typical.

RESULTS

Clinical characteristics: The clinical and electrophysiologic characteristics of the 7 patients are listed in Table I. Atrio-His (AH) and HV intervals were normal in all patients except in 1 who had a slightly prolonged AH interval.[19] Two-to-one block in the His-Purkinje system occurred at cycle lengths of ≤400 ms in 3 patients and >400 ms in 4 patients. According to the criteria of Josephson and Seides[19] the former values were considered to be within normal limits, and the latter abnormally prolonged.

Episodes: In all, 20 episodes of progression of 2:1 AV block were identified in the 7 patients: All were seen at pacing cycle lengths and AA intervals shorter than those at which stable 2:1 HV (and AV) block had appeared. However, the HH intervals were longer than the corresponding stimulus-stimulus and AA intervals due to the development of rate-dependent AH (AV nodal) Wenckebach periods.

Typical episodes: Thirteen episodes were typical.[1,9,10] Two-to-one progressed to 3:1 AV block when AH Wenckebach periods coexisted with the preexisting 2:1 HV block, provided that: (1) the Wenckebach period was completed during inscription of an A deflection, which would otherwise had been conducted if the preceding sequence of 2:1 AV block had persisted; and (2) the interval between the H deflection of the last beat reaching the His bundle and the H deflection following the A deflection blocked at the AV node exceeded the HH interval at which 2:1 HV block had first appeared. For example, in Figure 1 (top panel), the pacing cycle length was 320 ms. It was recorded from a patient in whom 2:1 HV block had first appeared at a cycle length of 360 ms. Two-to-one increased to 3:1 AV block because: (1) the AH Wenckebach period started with A1 and was completed during inscription of A7, which would have been conducted had the preceding 2:1 sequence continued; and (2) the interval between the sixth and seventh H deflections (585 ms) exceeded the HH interval at which 2:1 HV block was detected (360 ms).

In these typical episodes the dynamic A(M):V(N) conduction ratios were (with the number of episodes in parentheses): 7:3 (3); 9:4(8) and 11:5(2). They thus conformed to the previously described universal formula

for conversion of 2:1 AV nodal block into 3:1 AV nodal block, namely, 2N + 1:N in which N was the second number of a ratio that during 1:1 AH block was represented as M:N.[15]

As previously reported, if a "proximal" Wenckebach period is completed after inscription of a deflection which would have blocked if the preceding 2:1 sequence had continued, the 2:1 block does not progress to 3:1 block.[3,10] On the contrary, 2:1 block persists, but with a different (shorter) AV interval. This explains why, in Figure 1 (bottom panel), after the AH Wenckebach period ended with A4, 2:1 AV block continued, but with an AV interval (160 ms) shorter than the preceding AV interval (210 ms).

Atypical episodes: Seven atypical episodes were identified (Table I). Figure 2 shows an episode of 2:1 block progressing to 4:1 AV block with a run of 3:1 AV block in between. Two-to-one HV block had appeared, during sinus rhythm, at a cycle length of 780 ms (Table I). Note that with stimulus-stimulus and AA intervals measuring 350 ms, the entire episode consisted of AH Wenckebach periods coexisting with HV block. In this case several atypical features occurred. Initially, 2:1 increased to 3:1 AV block despite the first AH Wenckebach period ending with the inscription of a deflection (A4) that had been unable to reach the ventricles during the previous 2:1 sequence. Nevertheless, 3:1 AV block resulted because the next His deflection appeared at an (H4) interval (520 ms) that was shorter than 780 ms. Consequently, in contrast to Figure 1 (bottom panel, where the reverse occurred) 3:1 AV block ensued.

Immediately after this, 3:1 increased to 4:1 AV block, thus not regressing to 2:1 AV block. The latter resulted from a combination of factors. First, concealed conduction must have occurred within the His-Purkinje system.[20] Such a phenomenon explains why, despite the fact that the interval between H5 and H7 (810 ms) exceeded 780 ms, H7 was unable to reach the ventricles. For it to take place H6 should have had an extent of concealed penetration into the distal His-Purkinje system capable of preventing transmission of H7.[21] Second, the coexisting AH Wenckebach period was terminated during inscription of the subsequent A deflection (A9) that otherwise would have been able to reach the

ventricles. In this case, considering the entire sequence of 2:1 to 3:1 to 4:1 AV block as 1 episode yielded a total A:V (or M:N) ratio of 9:3.

A different type of atypical episode is shown in Figure 3 since 2:1 decreased to 3:2 block which *then* progressed directly to 3:1 AV block. Two-to-one HV block had first appeared at a pacing cycle length of 360 ms. At a shorter pacing cycle length (300 ms) regression to 3:2 AV block took place (Figure 3, top panel) when (after persistent 2:1 AV block up to A4) a 3:2 AH Wenckebach period reoccurred. Three-to-two AV block was possible because the degree of pacing-induced AH delay resulted in an H5H6 interval >360 ms.

Figure 3 (bottom panel) shows conversion of 3:2 *directly* to 3:1 AV block (the last A1 in the top panel is reproduced as the first A1 in the bottom panel). There are 2 consecutive AH Wenckebach periods. However, only the second period leads to 3:1 AV block because:

(1) the second A deflection of this period (A5) arrived at the His bundle at an (H3H4) interval of 360 ms, therefore being unable to reach the ventricles and; (2) the subsequent A deflection (A6) was blocked at the AV node. The total A:V (M:N) ratio in this episode was 6:3 (3:2 + 3:1).

Other types of atypical episodes were seen in a case where 2:1 HV block occurred at pacing cycle lengths ranging from 470 to 400 ms (patient 7). These episodes were identified at an even shorter cycle length (350 ms, Figure 4) when 4:2 AV block resulted from the coexistence of a 4:3 AH Wenckebach period with 3:2 HV block. Note the prolonged HV interval (100 ms) preceding the second (wide) QRS complex. According to Halpern et al,[21] episodes of 4:2 Mobitz type II block occur when the second atrial impulse of the episode is conducted during the supernormal period of the His-Purkinje system. In Figure 4 it is possible to postulate

FIGURE 1. Surface and intracavitary leads in a typical episode of conversion of 2:1 to 3:1 atrioventricular (AV) block *(top panel)*. A 7:6 atrio-His (A-H) Wenckebach period coexisted with 2:1 His-ventricular (H-V) block. In the *ladder* diagram, numbers (expressed in ms) at the A-H and H-V levels represent conduction times through the AV node and His-Purkinje system, respectively, whereas those at the His bundle (H) level indicate intervals between the corresponding consecutive H deflections. *Bottom panel,* the 4:3 A-H Wenckebach period was completed during inscription of an A deflection (A4), which would have been blocked at the His-Purkinje system if the previous 2:1 sequence had persisted. This did not result in 3:1 AV block, but in persistence of 2:1 AV block with a decrease in AV conduction time from 210 to 160 ms (as indicated here by numbers in the V level). DCS = distal coronary sinus electrogram; HBE = His bundle electrogram; S = stimulus artifact.
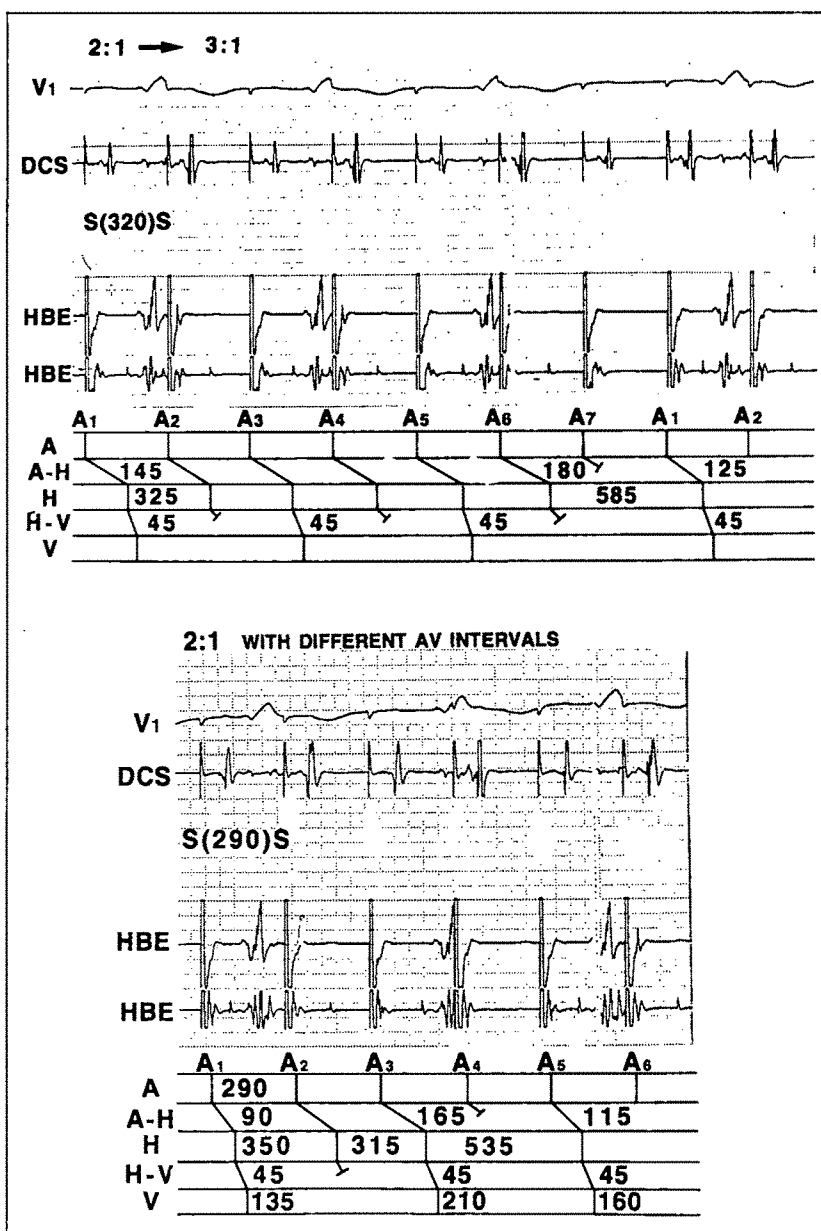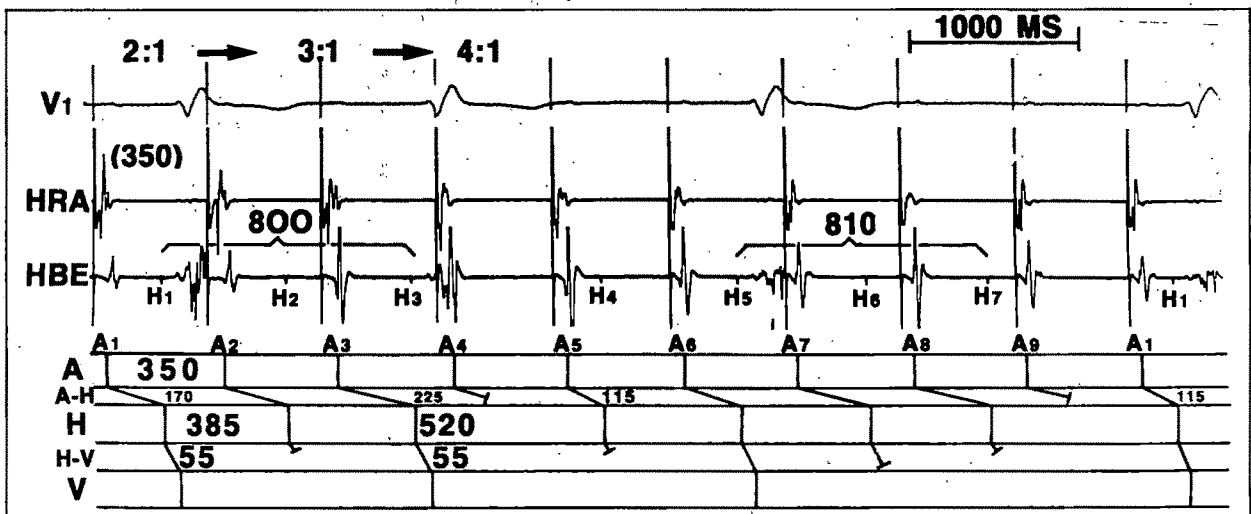
FIGURE 2. Atypical episode of conversion of 2:1 to 4:1 atrioventricular block, with a run of 3:1 block in between. There is documented 2-level block during which atrio-His (AH) Wenckebach periods coexist with His-Purkinje conduction disturbances. The fifth atrial deflection (A5) was blocked at the His-Purkinje system because it occurred during its effective refractory period, whereas A8 could not reach the ventricles because of the concealed penetration of A7. See text. HBE = His bundle electrogram; HRA = high right atrium; H-V = His-ventricular.
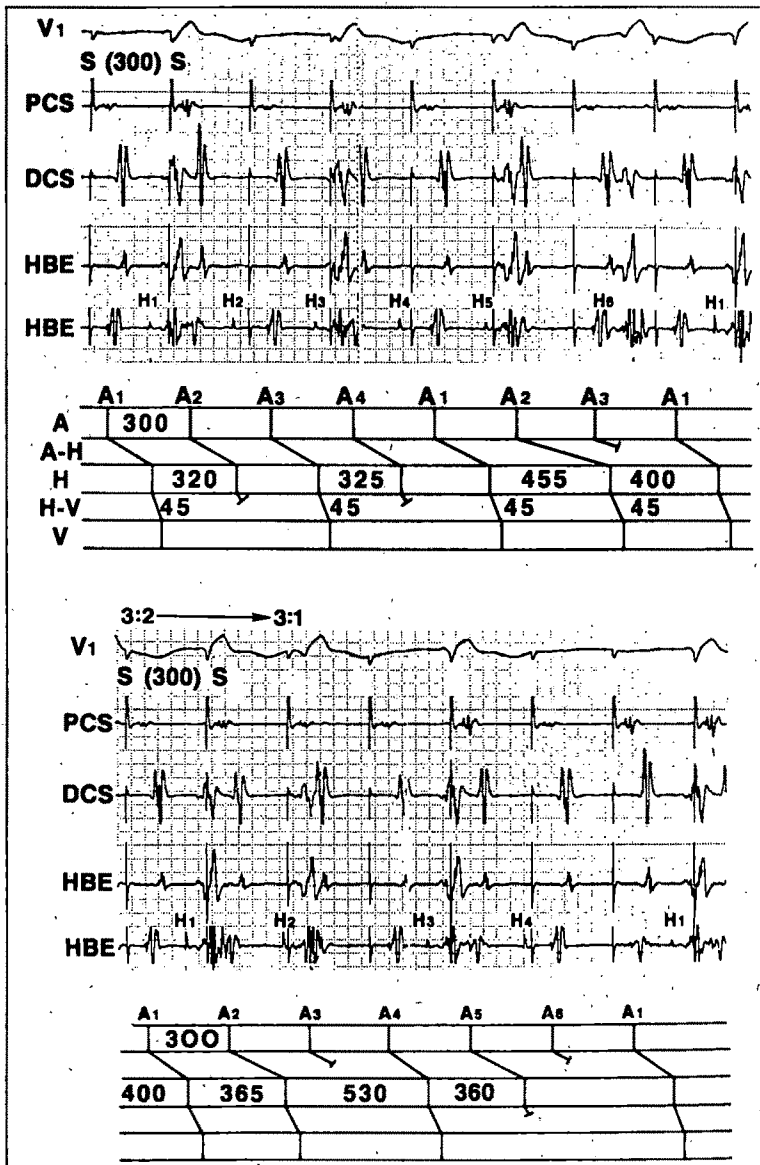
FIGURE 3. Documented 2-level block with regression of 2:1 to 3:2 atrioventricular block *(top panel).* Thereafter, an atypical episode resulted, since 3:2 converted directly into 3:1 atrioventricular block *(bottom panel).* The last atrial deflection (A1) in the *upper panel* is reproduced as the first A1 in the *bottom panel.* PCS = proximal coronary sinus; other abbreviations as in Figures 1 and 2.

transverse disassociation of the latter into a more proximal and a more distal level, as depicted in the left-sided diagram. If 2:1 HV block had been occurring at the proximal level (having a short or absent relative refractory period), arrival of excitation during its supernormal period could allow the impulse to reach a distal level, one possessing a longer relative refractory period. This would allow the impulse to activate the ventricles, but with delay. However, other explanations are possible. For example, with 4:3 AH Wenckebach, (as represented in the right-sided diagram) coexistence of a 3:2 HV Wenckebach, or, simply, occurrence of H2 during the relative refractory period of the His-Purkinje system may have resulted in a (total) 4:2 A:V (M:N) ratio. Yet, the latter explanations are unlikely because H2, occurring after a long preceding HH interval, would be expected to appear during a longer effective refractory period of the His-Purkinje system. Regardless as to why H2 arrived at the ventricles, H3 was blocked because of its inscription at an even shorter HH interval. Finally, A4 ending the 4:3 Wenckebach period was blocked at the AV node, thus completing the episode of 4:2 AV block. In the atypical episodes the A(M):V(N) ratios were 6:3 once, 9:3 in 3 episodes and 4:2 in 3 episodes (Table I).

DISCUSSION

Mechanisms of pacing-induced progression of 2:1 AV block into higher degrees of AV block during documented coexistence of AV nodal and His-Purkinje conduction disturbances: Most reports discussing progression of 2:1 AV block attributed to multilevel block have included patients with sinus, or rapid atrial, rhythms in whom the various levels were inferred to be located (but not directly observed) at the AV node.[3,4,9,11,12,20,22,23] Fewer studies have analyzed progression of pacing-induced 2:1 AV block in which 2 levels of block were, by electrophysiologic studies, seen to occur in 2 separate

structures (AV node and His-Purkinje system). In previous studies where His bundle recordings were performed, typical episodes of conversion of 2:1 into 3:1 AV block were attributed to the association of a proximal AH Wenckebach period with a distal 2:1 HV block (Figure 1).[1,5,6,8-11] Progression of 2:1 into 4:1 AV block was ascribed to the coexistence of a proximal 2:1 block with a distal Wenckebach period.[1,5,9-11] However, the present communication shows that other mechanisms may be involved. Thus, 2:1 increasing to 3:1 AV block was also noted (Figure 2) when the A deflection (A5) that would have been conducted if the 2:1 sequence had persisted reached the His bundle at an HH interval shorter than the one at which 2:1 HV block first appeared (most likely during the effective refractory period of the His-Purkinje system). This contrasts with what was seen in Figure 1.

Furthermore, 3:1 AV block also could emerge *directly* from 3:2, not 2:1, AV block (Figure 3). Moreover, progression from 2:1 to 4:1 occurred with a run of 3:1 AV block in between. This was possible (Figure 2) after the 2:1 progressed to 3:1 (in the atypical mode previously discussed), because the H deflection, which would have been conducted if the 3:1 sequence had continued, was blocked in the His-Purkinje system (due to the concealed penetration of the previous H) and the subsequent A was blocked at the AV node (because it ended an AH Wenckebach period). Concealed conduction into the His-Purkinje system was previously postulated by Halpern et al[21] to explain block of the third impulse of 5:2 episodes of Mobitz type II AV block.

Another interesting finding was observing episodes of 4:2 AV block at pacing cycle lengths shorter than those resulting in 2:1 HV block (Figure 4). Although these episodes have been reported during block occurring in a single structure (the His-Purkinje system),[21] in our case they were seen in 2 separate structures (Figure 4). However, the mechanisms of conduction of the sec-

FIGURE 4. Episodes of 4:2 atrioventricular block during documented 2-level block resulting from the association of 4:3 atrio-His (A-H) Wenckebach with 3:2 His-ventricular (H-V) block. *Left side* of the diagram depicts supernormal conduction of H2 (stimulus artifact [S] at the H-V level) in the upper part of a transversely dissociated His-Purkinje system. *Right side* offers an alternate interpretation: 3:2 Wenckebach within the His-Purkinje system. The first and second H-V intervals of each episode measured 55 and 100 ms, respectively. Other abbreviations as in Figures 1 to 3.
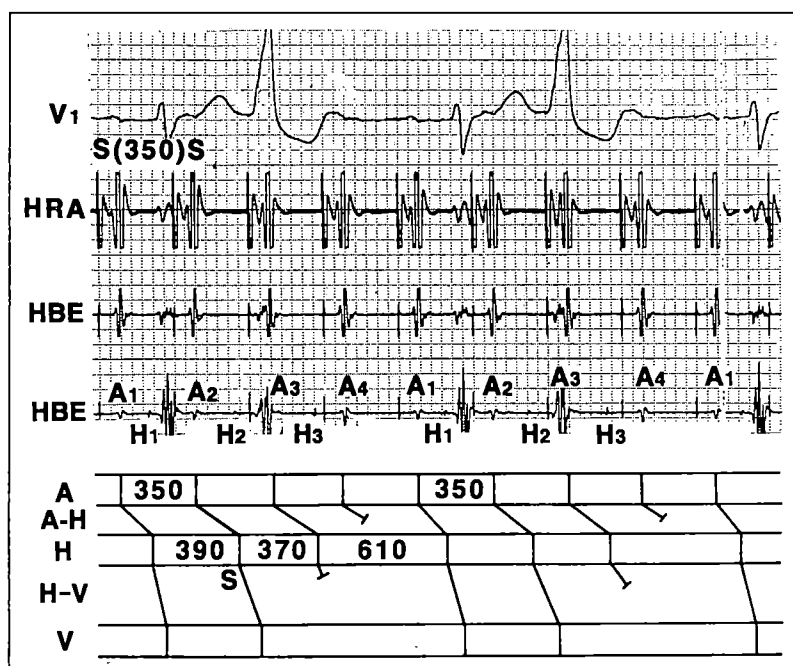
ond H deflection, following a long preceding HH cycle, are unclear. In the cases of Halpern et al[21] this finding (called paradox 2) "consisting of the fact that P2 is conducted following a long cardiac cycle (when His-Purkinje system refractoriness is expected to last longer)" was attributed to supernormal conduction. In addition, these investigators believed that with faster rates the possibilities of "hitting" the supernormal period were also greater. A 4:2 stimulus-to-response block was also attributed to supernormality in the experimental studies of Chialvo and Jalife[24] where Purkinje fibers were stimulated.

But in the cases of Halpern et al, where supernormality was postulated, the HV intervals were similar to, or shorter but not longer than, the basic HV intervals. Still, supernormality may be invoked as depicted in the left-sided diagram of Figure 4, by postulating 2-level block in the His-Purkinje system as proposed by Halpern et al[21] to explain their Figure 8 and Castellanos et al[19] for the interpretation of their Figure 1.

Comparison between the dynamics of progression 2:1 AV block occurring exclusively at the AV node with those of 2:1 AV block resulting from coexisting AV nodal and His-Purkinje system conduction disturbances: Shrier et al[13] observed at the AV node what had been previously described in a mathematic model, namely, that if there was an M:N (A:V) rhythm at one frequency and an M':N' rhythm at a second frequency, then there would be an M + M':N + N' rhythm at an intermediate frequency.

In our previous studies of the dynamics of pacing-induced 2:1 AH block, progression to 3:1 AH block was seen with ratios (5:2, 7:3, 9:4, 11:5, and so forth), which could invariably be represented by a universal 2N + 1:N formula.[15] Similarly, at a constant cycle length, conversion of 2:1 to 4:1 AH block occurred only directly (without an intermediate run of 3:1 block) with ratios (6:2, 8:3, 9:4, and so forth) invariably represented by a universal 2N + 2:N formula.[15]

At the human AV node, once stable 2:1 AH block (represented by a general 2 N:N ratio) was achieved, a further decrease in pacing cycle length caused an increase in the degree of AH block, not a decrease to 3:2 AH block.[14] Moreover, 3:2 did not progress directly to 3:1, but to 2:1 AH block. On the other hand, according to Halpern et al,[21] 2:1 Mobitz type II AV block exclusively taking place in the His-Purkinje system could evolve to 3:2 or progress to 4:2 and 5:2 AV block provided that supernormal conduction was present. In this study of documented 2-level block, typical episodes of progression of 2:1 to 3:1 HV block produced ratios that could (as at the AV node) be represented by the general 2N + 1:N ratio.[15] Not surprisingly, atypical episodes yielded ratios that at the AV node would have to be represented differently. For example, 3:2 to 3:1 AV block (Figure 3) occurred with a 6:3 ratio. Similarly, the ratio of the 2:1 to 3:1 to 4:1 AV episode was 9:3. At the AV node these ratios would have to be represented by 2N:N and 3N:N, respectively. The former would be indicative of stable 2:1 AV block and the latter of either stable 3:1 AV block (3:1 + 3:1 + 3:1 = 9:3) or of con-

version of 2:1 directly into 5:1 AV block (2:1 + 2:1 + 5:1 = 9:3).[15]

Finally, episodes of 4:2 AV block were not observed at the AV node at pacing cycle lengths shorter than those yielding 2:1 stable AV block.[13,25] During incremental pacing they were reported before stable 2:1 AV block developed.[25] When occurring after development of stable 2:1 AV block, the 4:2 AV ratio seems to result exclusively from His-Purkinje conduction disturbances, either isolated as in Halpern's cases[21] or associated with AV nodal conduction disturbances, as in our cases.

Implications: Previously unreported mechanisms for progression of 2:1 AV block due to documented 2-level conduction disturbances were identified in only 7 consecutively studied patients. Thus, they may be more frequent than previously thought. Mechanistic and dynamic differences with what has been observed, during atrial pacing, at the human AV node, or exclusively at the His-Purkinje system can, obviously, be ascribed to the fact that several, diverse, coexisting phenomena could (and did) occur in 2 separate structures.[13,21] Emphasis should be placed on the fact that these mechanisms and dynamics apply only to what happens during incremental atrial stimulation. It is tempting to assume that these findings can be extrapolated to what occurs in nondocumented, but empirically postulated, 2-level AV nodal block in patients having spontaneous sinus rhythm with pathologic abnormalities of the AV conducting system, ectopic atrial rhythms, atrial flutter with varying AV conduction, and the so-called "paroxysmal atrial tachycardia with block." Moreover, and not surprisingly, other phenomena and different A(M):V(N) ratios are likely to be identified in the future when analyzing surface electrocardiograms, as well as during electrophysiologic evaluation. However, further studies are necessary to corroborate these assumptions.

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Electrocardiographic Abnormalities After Radiofrequency Catheter Ablation of Accessory Bypass Tracts in the Wolff-Parkinson-White Syndrome

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Repolarization abnormalities on surface electrocardiograms have been described after loss of ventricular preexcitation in some patients with the Wolff-Parkinson-White syndrome. Radiofrequency catheter ablation of overt accessory pathways provides a unique opportunity to study this phenomenon. In this study, serial electrocardiograms were obtained before and after radiofrequency ablation of manifest accessory pathways in 19 patients, of concealed accessory pathways in 6 and after radiofrequency atrioventricular nodal modification in 12. Seven patients undergoing manifest right-sided accessory pathway ablation had left superior frontal plane T-wave axis deviations after ablation ($-42 \pm 13°$). No patient with a manifest left-sided or concealed accessory pathway, or atrioventricular nodal modification had T-wave abnormalities after ablation; however, left anterior fascicular block and incomplete right bundle branch block each occurred in 1 patient with left accessory pathway ablation.

Repolarization abnormalities observed after ablation were similar to T-wave abnormalities during the absence of preexcitation before ablation and persisted up to 5 weeks after the procedure. Patients with repolarization abnormalities after ablation had significantly longer preexcited QRS durations than those without such changes, suggesting that the initial contribution of the pathway to ventricular activation is an important determinant of T-wave changes after ablation. The proposed mechanism for repolarization abnormalities after ablation is the phenomenon of T-wave "memory."

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In patients with the Wolff-Parkinson-White syndrome, ventricular repolarization abnormalities may be evident on surface electrocardiograms during spontaneous or induced suppression of ventricular preexcitation.[1] In the past, this phenomenon was observable only after cardiac surgery, administration of antiarrhythmic agents or stimulation of neurocardiac reflexes to abolish preexcitation.[1,2] However, each of these interventions may have independent effects on repolarization. The development of radiofrequency catheter ablation techniques provides a unique opportunity to study surface electrocardiographic patterns resulting from abrupt abolition of preexcitation in the absence of confounding pharmacologic or surgical influences. In this study, we analyzed serial surface electrocardiograms for T-wave abnormalities in 37 patients who underwent successful radiofrequency catheter ablation procedures to determine the prevalence and time course of electrocardiographic repolarization changes in these patients.

METHODS

Study group: Thirty-seven patients who underwent successful radiofrequency catheter ablation procedures at the University of Virginia Health Sciences Center were enrolled in the study. Patients with multiple accessory pathways or unsuccessful ablation procedures were excluded. Nineteen patients underwent successful radiofrequency catheter ablation of an extranodal accessory atrioventricular (AV) pathway and had evidence of intermittent or continuous preexcitation on surface electrocardiography. Six patients who underwent successful ablation of concealed accessory pathways and 12 who underwent successful radiofrequency AV nodal modification were selected as a comparison group. Accessory pathway function was defined as concealed if the patient had no documented electrocardiogram showing preexcitation and no anterograde accessory pathway conduction demonstrable during electrophysiologic studies. Patient characteristics by group are listed in Table I. All cardioactive drugs were discontinued 5 half-lives before the ablation procedures and withheld during follow-up.

Electrophysiologic testing: All procedures were performed in the fasting state with intravenous midazolam (2 to 5 mg) and fentanyl ($\leq$100 mg/hour) sedation. Preliminary electrophysiologic testing was performed in accordance with established protocols and criteria.[3] Atrial pacing and recording from multiple sites and adenosine injections were used to evaluate possible an-

TABLE I Characteristics of Study Group			
Group	Preexcited AP	Concealed AP	AVN Modification
No. of pts.	19	6	12
Age (yr)	32 ± 10	32 ± 11	49 ± 18
Men/women	14/5	2/4	4/8
Ablation site			
Right anteroseptal/posterolateral	2/4	0/1	Slow 5
Right free wall	1	0	Fast 7
Left posterior	3	2	
Left posterolateral	3	2	
Left lateral	6	1	
No. of lesions	4 ± 3	3 ± 1	4 ± 3
Voltage (V)/current (mA)	51 ± 5/420 ± 32	51 ± 6/397 ± 20	56 ± 5/399 ± 45

Values are presented as mean ± SD.
AP = accessory pathway; AVN = atrioventricular node.

terograde and retrograde conduction patterns for evidence of accessory pathway function. Patients undergoing AV nodal modification demonstrated dual AV nodal physiology and had typical sustained AV nodal reentrant tachycardia induced with programmed electrical stimulation. Radiofrequency energy (RFG-3AV lesion generator, Radionics, Inc., Burlington, Massachusetts) was delivered to the endocardial sites using 6Fr steerable quadripolar catheters with a 7Fr tip diameter (Mansfield Corp., Watertown, Massachusetts)[4,5] and a large skin surface electrode. If preexcitation was lost or tachyarrhythmias terminated within the first 5 to 10 seconds of energy delivery, current was applied for 30 to 60 seconds. The average number of lesions (30- to 60-second duration) per patient is shown in Table I. Ablation procedures were defined as successful if complete abolition of anterograde and retrograde accessory pathway conduction or modification in AV nodal conduction properties associated with inability to induce AV reciprocating or AV nodal reentrant tachycardias was observed. Ablation procedures that produced these changes only transiently (<30-minute duration) were considered unsuccessful.

Surface electrocardiograms: Twelve-lead surface electrocardiograms were obtained immediately before ablation procedures, during induced tachycardias, immediately and 12 to 24 hours after ablation, and 4 days to 20 weeks after ablation (follow-up). Electrocardiograms obtained in the electrophysiology laboratory (i.e., immediately before and after ablation, and during tachycardias) had precordial lead V_3–V_6 positions displaced 1 to 2 intercostal spaces superiorly to the customary positions to accommodate self-adhesive defibrillation patches at the cardiac apex and limb leads attached to the deltoids and anterior iliac crests to minimize motion artifact. All other electrocardiograms were obtained using standard electrode configurations.

Mean QRS and T-wave vector orientations were determined by the electrocardiogram recorder computer analysis (Marquette MAC 15) or manual calculation based on relative vector magnitudes in orthogonal leads. All computer-derived values were overread for accuracy. Repolarization abnormalities after the procedure were defined as mean frontal plane T-wave axes <0° or >+90°, or negative T waves lateral to lead V_2.

RESULTS

Nine of 19 patients with manifest preexcitation (47%) demonstrated electrocardiographic abnormalities after ablation. All 7 patients with preexcitation undergoing right-sided accessory pathway ablation had abnormal left superior mean frontal plane T-wave vector orientation (−42 ± 13°) despite normal mean QRS vectors (+50 ± 27°). Furthermore, 1 patient also had T-wave inversion in lead V_6. An example of these changes is shown in Figure 1. No ST-segment deviations from the isoelectric baseline accompanied T-wave inversions in any lead. One patient also had incomplete right bundle branch block after ablation. Of 12 patients with manifest preexcitation undergoing left-sided accessory pathway ablations, left anterior fascicular block and right bundle branch block developed in 1 patient each. No patient with a left-sided accessory pathway demonstrated T-wave abnormalities after ablation. No patient with a concealed accessory pathway ablation or an AV nodal modification developed conduction or repolarization abnormalities (Figure 2).

The electrocardiographic abnormalities mentioned previously were observed immediately after ablation in all but 2 patients. One patient had intermittent preexcitation during the 6 hours after the procedure. T-wave abnormalities were observed 11 hours after ablation. In another patient, the T wave became inverted in lead III and biphasic in lead aVF immediately after ablation, and was inverted in leads II, III and aVF on the 12-hour recording. This patient had received procainamide (which suppressed preexcitation) to convert atrial fibrillation that occurred during the study.

By 12 to 18 hours after ablation, both right bundle branch block patterns had resolved, whereas the left anterior fascicular block had partial resolution. All isolated T-wave abnormalities were still present at 12 to 24 hours after development. Late follow-up electrocardiograms (4 days to 16 weeks) were available in 6 of 7 patients with T-wave abnormalities and showed persistent changes for up to 5 weeks in 2 patients, whereas resolution of these abnormalities occurred by 4 weeks in 2 patients (Figure 3). Preexcitation recurred in the remaining 2 patients.

Loss of preexcitation during AV reciprocating tachycardia or rapid atrial pacing at a cycle length
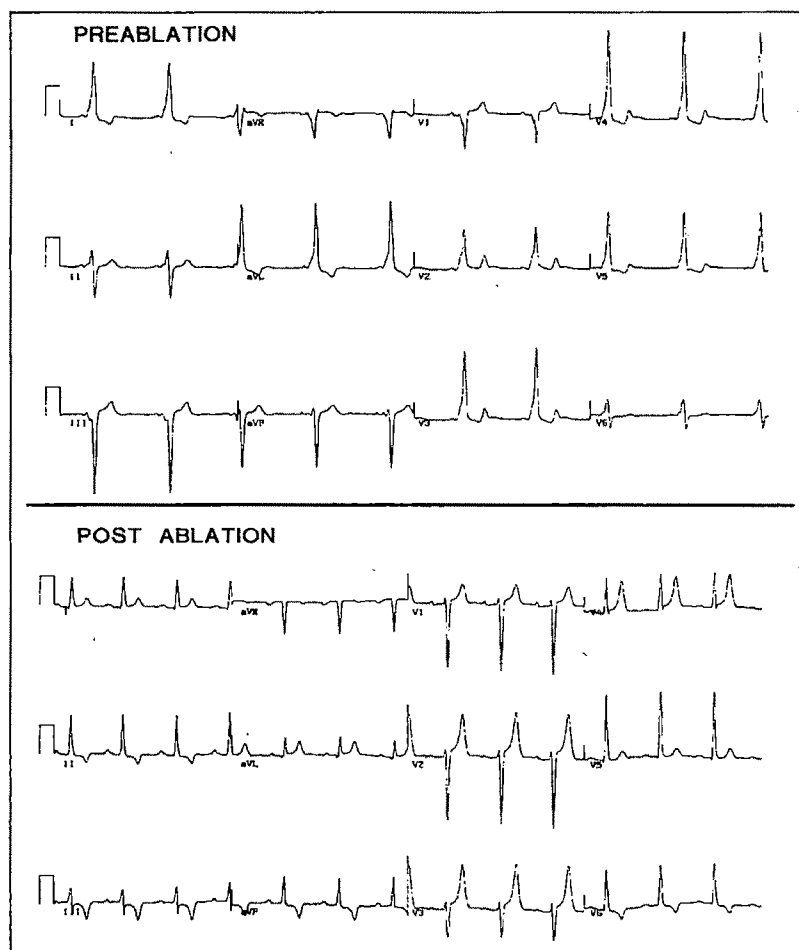
FIGURE 1. Surface 12-lead electrocardiograms obtained before *(top panel)* and after *(bottom panel)* ablation of right posteroseptal accessory pathway in 25-year-old man. Preablation *tracing* demonstrates typical ventricular preexcitation. Postablation *tracing* shows marked T-wave inversion in leads II, III, aVF and V_6.
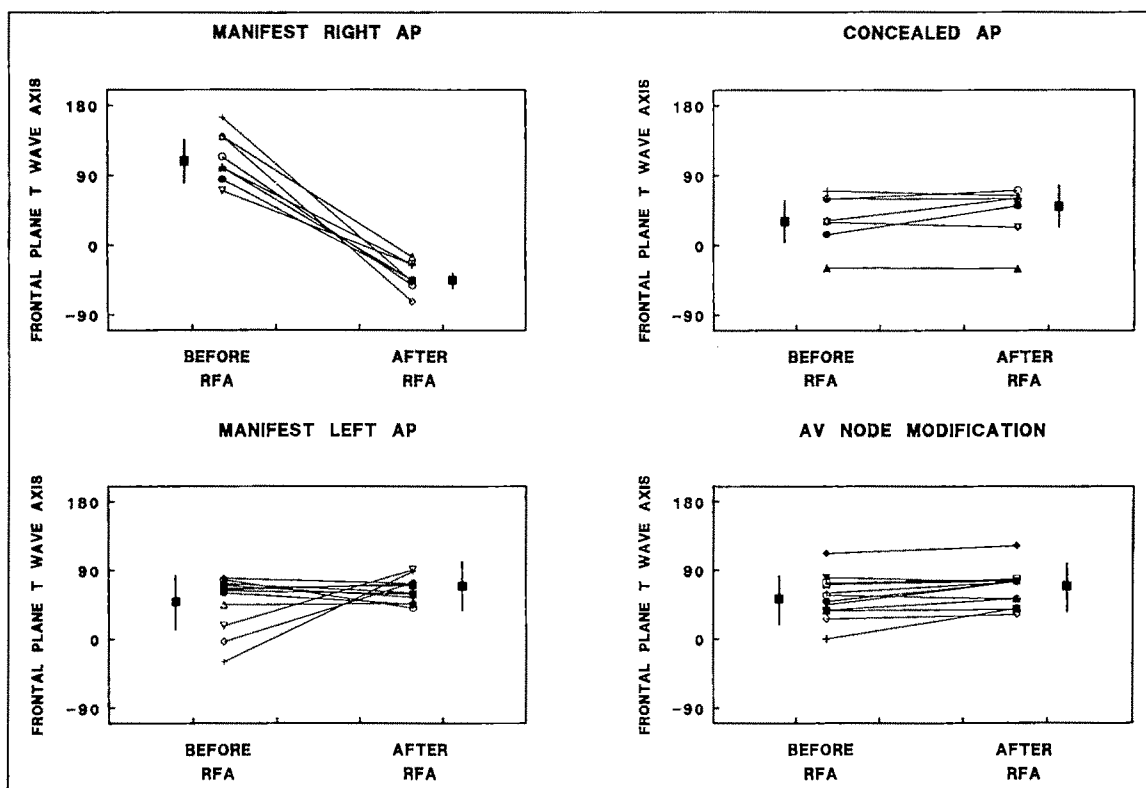
FIGURE 2. *Graphs* showing frontal plane T-wave axes before and after ablation for 38 patients according to location and type of ablated pathway (AP). Mean ± SD points for each group are also shown. AV = atrioventricular; RFA = radiofrequency ablation.

shorter than the accessory pathway effective refractory period reproduced T-wave changes similar to those seen after ablation in 6 of 7 patients (Figure 4). In the remaining patient, loss of preexcitation before ablation was not observed. Of the 10 preexcited patients without electrocardiographic changes after ablation, only 1 had an electrocardiographic finding (left bundle branch block aberrancy) during AV reciprocating tachycardia or rapid atrial pacing that was not present after ablation. Of the 18 control patients, 2 (1 concealed accessory pathway and 1 AV nodal reentry) had leftward T-wave vector shifts during reentrant tachycardias.

Previous studies suggested that the appearance of repolarization abnormalities after loss of preexcitation may depend on the magnitude of ventricular preexcitation.[1,6] Therefore, we compared preexcited QRS durations on electrocardiograms before ablation between patients with and without repolarization abnormalities (Figure 5). Patients with T-wave abnormalities after ablation had significantly longer preexcited QRS durations than did those with no such changes.

DISCUSSION

The appearance of repolarization abnormalities after induced or spontaneous suppression of preexcitation in the Wolff-Parkinson-White syndrome was first described in 1966.[7] In a subsequent study of this phenomenon by Nicolai et al,[1] procainamide, ajmaline or eyeball pressure was used to suppress preexcitation in 45 patients. The present study demonstrates left-axis T-wave deviation after radiofrequency catheter ablation of

each of the 7 right septal or free-wall accessory pathways, with intermittent or continuous anterograde function. These repolarization abnormalities persisted for up to 5 weeks of follow-up. The electrocardiographic repolarization abnormalities after ablation were also evident
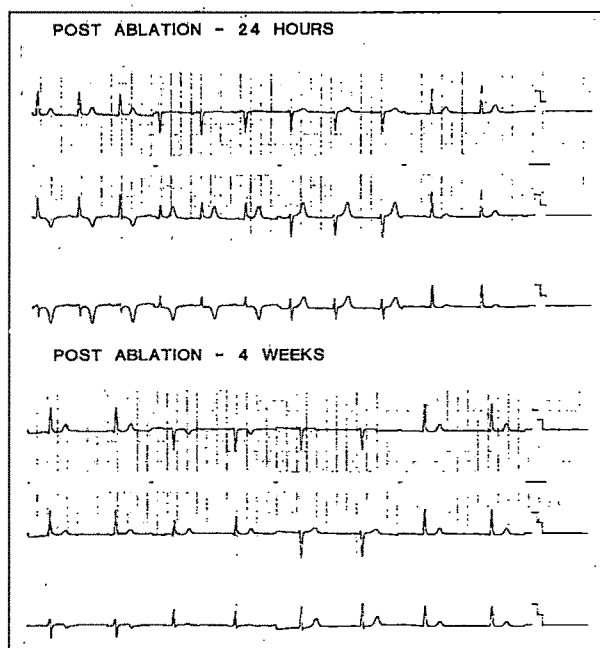
FIGURE 3. Electrocardiograms from same patient as in Figure 1 showing persistent T-wave inversions in leads II, III and aVF 24 hours after ablation *(top panel)*, but resolution of T-wave abnormalities at 4 weeks after ablation *(bottom panel)*.

FIGURE 4. Electrocardiograms from same patient as in Figure 1 during orthodromic reciprocating tachycardia *(top panel)* demonstrating inferior and lateral T-wave abnormalities closely corresponding to those observed after radiofrequency ablation *(bottom panel)*. SVT = supraventricular tachycardia.
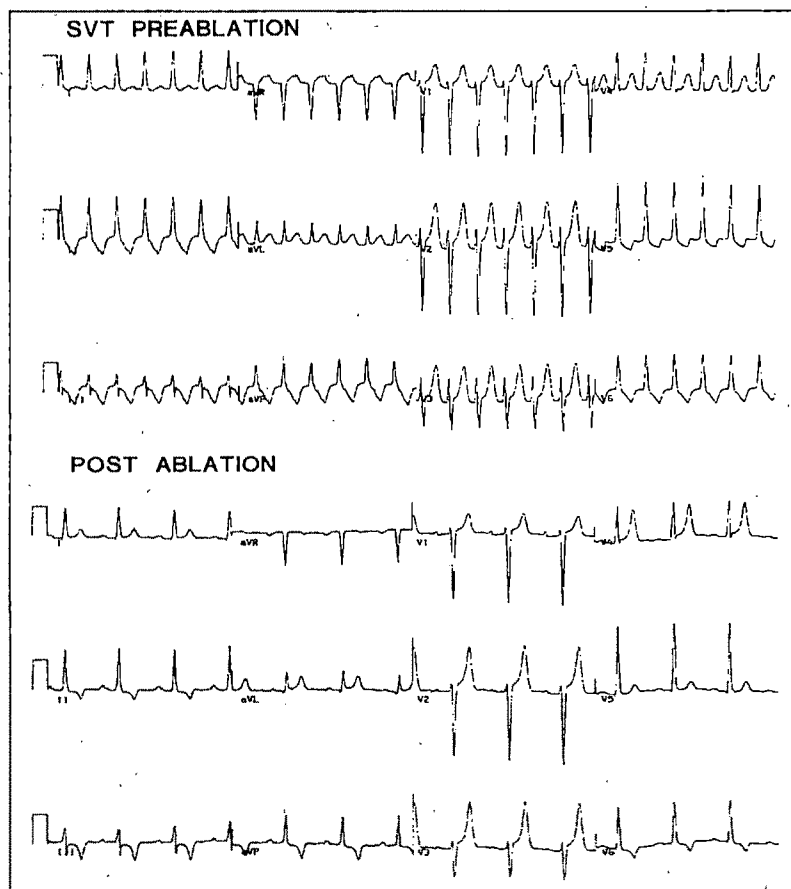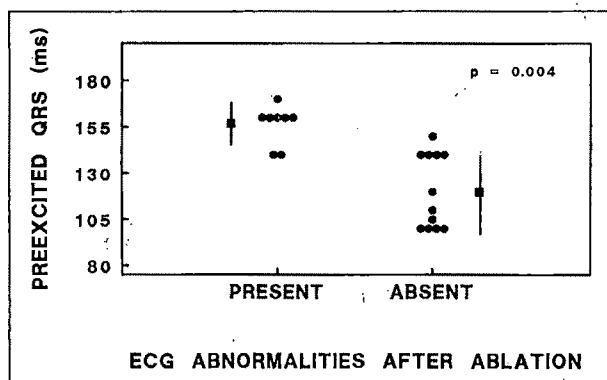
FIGURE 5. *Graph* comparing preexcited QRS durations before ablation on baseline electrocardiograms between patients with and without T-wave abnormalities after ablation. ECG = electrocardiographic.

during orthodromic AV reciprocating tachycardia or atrial pacing at a cycle length shorter than the accessory pathway refractory period. In contrast, the only changes observed in patients with left-sided pathway ablations were 2 transient conduction abnormalities after ablation. T-wave changes after ablation were not seen in any patient with AV nodal modification or concealed accessory pathway ablation. These changes may be confused with those due to coronary ischemia, such as could be caused by coronary artery injury or spasm as a result of ablation.

The mechanism responsible for T-wave changes after ablation is uncertain. Electrocardiographic repolarization abnormalities have been described after resolution of left bundle branch block and termination of ventricular pacing, as well as after loss of ventricular preexcitation.[7] Studies by Franz et al,[8] Costard-Jäckle et al[9] and other investigators suggested a common mechanism linking these phenomena by demonstrating that the timing and pattern of ventricular depolarization can profoundly influence the sequence of ventricular repolarization. In human subjects, Rosenbaum et al[6] demonstrated vectoral T-wave abnormalities after pacing related in orientation and duration to the site and duration of ventricular pacing. Using isolated rabbit hearts, Constrad-Jäckle et al[9] demonstrated an inverse relation between regional myocardial activation time and the action potential duration in the same area. Franz et al[8] demonstrated similar findings during detailed intraoperative mapping of human hearts. The concept of electrotonic interactions or modulation of repolarization has been proposed to explain these findings (i.e., sequentially depolarized myocardium invokes an interplay of electromotive forces [or currents] between fibers at different potentials).[9,10] Electromotive forces may act to prolong action potential duration at sites of earliest

myocardial activation and shorten action potential duration at sites of later depolarization. Time-dependent modulation and rectification of currents and resistances across intercellular cardiac gap junctions may sustain a particular repolarization sequence even after the original depolarization pattern is altered.

The data suggest that repolarization abnormalities after radiofrequency accessory pathway ablation result from abrupt alteration of the sequence of ventricular depolarization and are not a direct result of the radiofrequency lesion itself. This conclusion is supported by the occurrence of repolarization abnormalities only in patients with preexcitation and the appearance of similar T-wave abnormalities in nonpreexcited electrocardiograms before ablation. Similar findings and conclusions were recently described by Kalbfleisch et al.[12] The absence of T-wave changes after left-sided accessory pathway ablation in this series is curious, but may be explained by lesser degrees of ventricular preexcitation due to later activation of left-sided accessory pathways during sinus rhythm as compared with that of right-sided pathways, and not as a direct consequence of the position of the radiofrequency lesion.

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Improved Detection of Accessory Pathways that Bridge Posterior Septal and Left Posterior Regions in the Wolff-Parkinson-White Syndrome

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To improve the detection of accessory pathways that bridge the posterior septum and left posterior free wall, catheter maps of the coronary sinus from 21 patients (group I) who needed dissection of both these anatomic regions were compared with data from 23 (group II) with pathways confined to the posterior septum and from 9 (group III) with left posterior pathways. A decapolar catheter was used to map the coronary sinus in 0.5 to 1 cm steps. Intraoperative mapping was performed with a 16-electrode band. Catheter maps during atrial pacing and orthodromic supraventricular tachycardia were analyzed for the site of earliest activation and for differences in a new directional measure of conduction time between adjacent mapping sites. The site of earliest activation alone did not distinguish accessory pathways that bridged both anatomic regions, because 14 of 21 patients (66%) in group I would have been misclassified to either group II or III. In contrast, anterograde and retrograde directional conduction times distinguished patients in group I from those in groups II (p <0.01 to <0.0003) and III (p <0.04 to <0.0001). A multivariate model that incorporated the observed differences in directional interelectrode conduction times improved the identification of group I patients, with a sensitivity of 87% and a specificity of 90%. The results define new features in activation patterns measurable during catheter mapping that identify accessory pathways that bridge the posterior septum and left posterior free wall.

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The success of catheter[1,2] or surgical[3] ablation in patients with Wolff-Parkinson-White syndrome needs the accurate localization of accessory pathways. Atrial and ventricular insertions of accessory pathways have been traditionally identified based on earliest activation during orthodromic supraventricular tachycardia and maximal preexcitation, respectively.[4,5] Recordings of pathway potentials have further facilitated their localization.[6] However, accurate identification of accessory pathways that bridge the posterior septum and left posterior free wall is difficult. The purpose of this study was to determine the extent to which a new, directional measure of conduction time between adjacent mapping sites distinguishes these accessory pathways from those confined to the posterior septum or left posterior free wall.

METHODS

Patients: Preoperative and intraoperative maps from 21 patients (group I) with Wolff-Parkinson-White syndrome and accessory pathways that bridged the posterior septum and left posterior free wall who needed a combined dissection of both anatomic regions were compared with the data from 23 (group II) with pathways confined to the posterior septum and from 9 (group III) with accessory pathways located at left posterior sites. All accessory pathways in the 53 patients studied between November 1983 and October 1990 were divided successfully. There were 22 male and 31 female patients (aged 11 to 60 years, mean 28 ± 11). Associated structural heart disease was present in 18 patients (33%).

Preoperative catheter mapping: Studies were performed with patients in the postabsorptive, nonsedated state after they gave informed written consent. All antiarrhythmic drugs were discontinued ≥48 hours before the study. Multi-electrode catheters were positioned initially at the high right atrium, atrioventricular junction and right ventricular apex, and within the coronary sinus. Intracardiac electrograms and surface electrocardiographic leads I, aVF and V1 were recorded simultaneously and printed on an ink-jet recorder at paper speeds of 100 and 200 mm/s. Details of the stimulation protocol were previously published.[7–9]

Catheter mapping of the coronary sinus was performed with a 6Fr decapolar catheter (Bard Electrophysiology), with 2 mm interpole spacing and 1 cm spacing between each bipolar pair. The coronary sinus was partitioned into 6 regions (Figures 1 and 2) extending from the os to the left posterolateral wall. Coro-
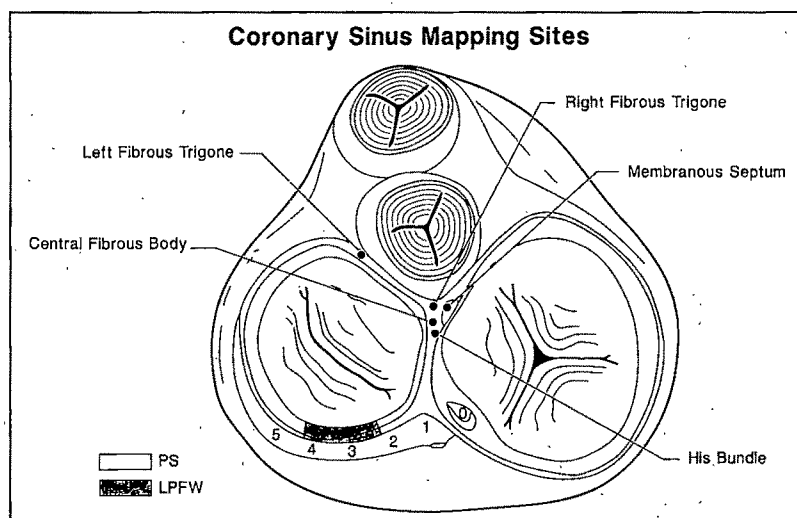
FIGURE 1. Stylized cross section of heart at level of atrioventricular groove illustrating mapping sites pertinent to this study. Coronary sinus has been partitioned into 6 regions extending from os to posterolateral wall. Posterior septum (PS) includes sites 0, 1 and 2. Left posterior free wall (LPFW) begins at site 3. Accessory pathways that bridged these 2 anatomic regions occurred between mapping sites 2 and 3. Site 3 is 2.5 to 3.0 cm from os of coronary sinus.

nary sinus mapping was performed by first advancing the decapolar catheter as far distal as possible and then withdrawing the catheter in 0.5 cm steps until the proximal electrode pair was at the os of the coronary sinus.[7-9] The intersection of the His bundle and the coronary sinus catheters in a left anterior oblique projection, as well as electrogram features, were used to identify the os of the coronary sinus.

Data analysis: Retrograde atrial activation was analyzed during orthodromic supraventricular tachycardia and expressed as ventriculoatrial intervals measured from the onset of the QRS complex in the surface electrocardiogram to the first major deflection of each local atrial electrogram. Directional conduction times between adjacent coronary sinus mapping sites were calculated by subtracting the activation time at the more

proximal mapping site from that at the more distal site (Figure 3). A positive value indicated activation moving leftward and away from the os of the coronary sinus, and a negative value indicated activation moving toward the os.

Anterograde ventricular activation was analyzed during atrial pacing that resulted in maximal preexcitation. For each electrode site, the interval between the onset of the delta wave in the electrocardiogram and the
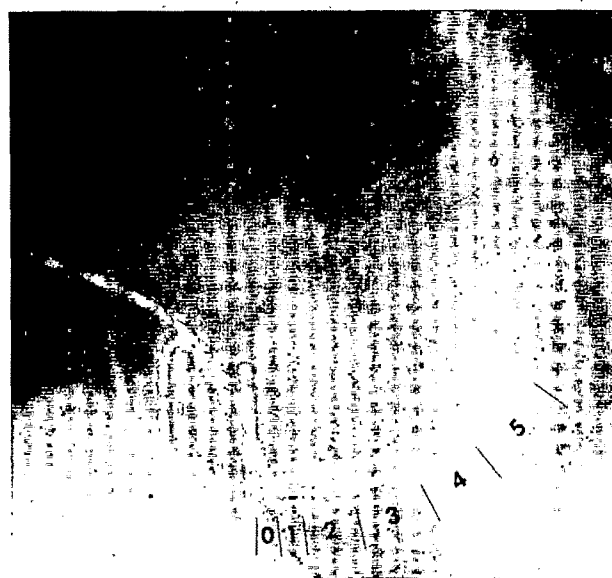
FIGURE 2. Radiograph of cardiac silhouette in 40° left anterior oblique projection. Decapolar mapping catheter is positioned in coronary sinus demonstrating 6 mapping sites (illustrated schematically in Figure 1). Distance between electrode pairs is 1 cm. Quadripolar catheters are positioned in high right atrium and right ventricular apex. Tripolar catheter is positioned at atrioventricular junction.
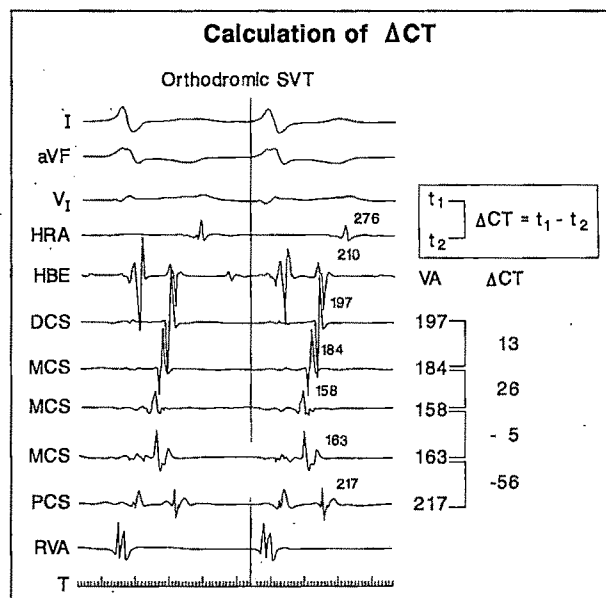
FIGURE 3. Representative data recorded during orthodromic supraventricular tachycardia (SVT). Leads I, aVF and V_1 from surface electrocardiogram, and intracardiac electrograms from high right atrium (HRA), atrioventricular junction, 5 coronary sinus mapping sites and right ventricular apex (RVA) are shown. Ventriculoatrial (VA) intervals were measured from onset of QRS complex. Difference in conduction times (ΔCT) between adjacent coronary sinus mapping sites was calculated by subtracting the activation time at the more proximal coronary sinus mapping site from the activation time at the more distal coronary sinus mapping site. DCS = distal coronary sinus; HBE = His bundle electrogram; MCS = mid-coronary sinus; PCS = proximal coronary sinus; T = 10 ms time lines; t_1 = VA time at distal coronary sinus mapping site; t_2 = VA time at proximal coronary sinus mapping site.

first major deflection of each local ventricular electrogram was measured. Directional conduction times between adjacent mapping sites were calculated by subtracting the activation time at the more proximal mapping site from that at the more distal site.

Intraoperative mapping: The computer-assisted mapping system was previously described in detail.[10-12] A nylon band with 16 bipolar button electrodes was positioned around the atrioventricular groove in each patient.[11] Ventricular and atrial activation were assessed during maximal preexcitation and orthodromic supraventricular tachycardia, respectively. Sites of earliest activation identified the ventricular and atrial insertions of the accessory pathways.

Surgical dissection: The decision to dissect the posterior septum or left posterior free wall, or both, was made after completion of intraoperative mapping and was based on data obtained from both the preoperative catheter and intraoperative maps.

Statistical analysis: Data were analyzed with the Statistical Analysis System.[13,14] Results are expressed as mean ± SEM. Repeated measures of analysis of variance using statistical contrasts provided within-group comparisons of adjacent retrograde and anterograde directional conduction times. Univariate predictors of group membership were determined by 1-way analysis of variance. Significant univariate factors were included in a stepwise logistic regression analysis that was implemented using the LOGISTIC procedure of the Statistical Analysis System. This approach provided estimates of sensitivity and specificity of predictions of

group membership. Estimates were based on a jackknife approach to reduce bias that is inherent in estimating parameters in the absence of an independent set of data with which to test the quality of estimates.

RESULTS

Between-group comparisons of directional conduction times: Figure 4 compares the mean directional conduction times measured along the coronary sinus during orthodromic supraventricular tachycardia from the 21 patients in group I with accessory pathways that bridged both the posterior septum and left posterior free wall with those from the 23 in group II with septal pathways and from the 9 in group III with left posterior free wall pathways. Directional conduction times measured for mapping sites 4 and 3, and 3 and 2 differed significantly between groups I and II. These observed differences were most marked (p = 0.0003) at sites 3 and 2, which were adjacent to the posterior septum. Directional conduction times measured for mapping sites 5 and 4, 4 and 3, and 2 and 1 also distinguished group I from III. Differences in atrial activation patterns between groups I and III were most marked (p = 0.0001) for mapping sites 4 and 3.

Similar differences in the patterns of ventricular activation during atrial pacing were observed in patients in group I that distinguished them from those in groups II and III (Figure 5).

Within-group comparison of directional conduction times: During orthodromic supraventricular tachycardia, absolute conduction times along the coronary sinus were relatively constant for patients in groups I and II (Figure 6). However, in both groups, significant differences in directional conduction times were observed. For patients in group I with pathways that bridged the pos-
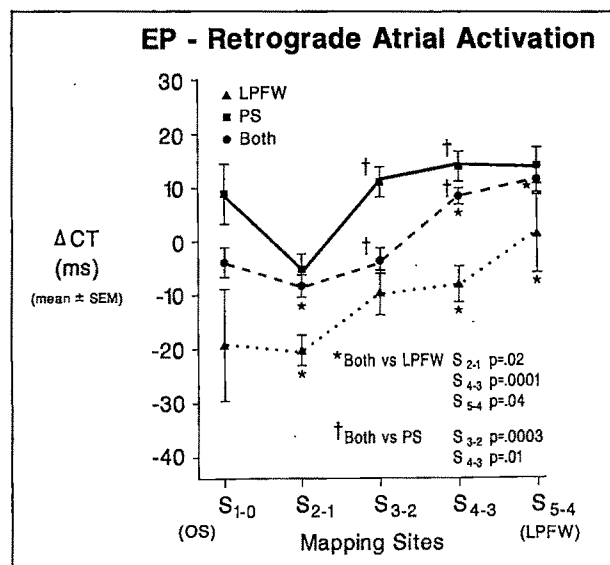
FIGURE 4. Comparison of directional conduction times (ΔCT) measured during orthodromic supraventricular tachycardia. Values for each patient group are plotted on *y* axis and represent mean ± SE (expressed in ms). Adjacent mapping sites from left posterolateral wall to os used to calculate directional conduction times are plotted on *x* axis. Patients with accessory pathways that bridged posterior septal space (PS) and the left posterior free wall (LPFW) could be distinguished from 2 groups with accessory pathways confined to either posterior septum or left posterior free wall at multiple coronary mapping sites. Negative value indicates conduction toward os and positive value conduction away from os. EP = electrophysiologic testing.
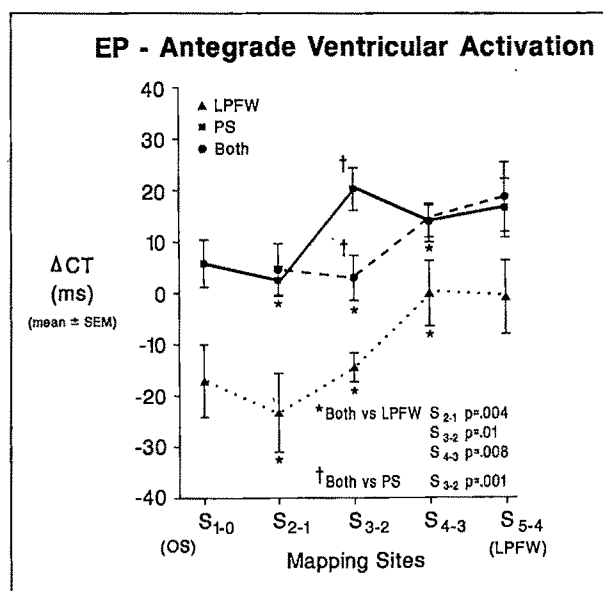
FIGURE 5. Comparison of directional conduction times (ΔCT) measured during maximal ventricular preexcitation. Figure is arranged in format similar to that of Figure 4. Directional conduction times at multiple mapping sites distinguished accessory pathways that bridged posterior septum (PS) and the left posterior free wall (LPFW) from other 2 groups. EP = electrophysiologic testing.

terior septum and left posterior wall, significant differences (p = 0.0007) in directional conduction times were observed between the more distal coronary mapping sites 4 and 3, and 3 and 2. Furthermore (and in contrast to group II with posterior septal pathways), the negative interelectrode conduction times reflecting activation toward the os of the coronary sinus spanned the first 3 mapping sites. For patients in group II with posterior septal pathways, significant differences (p = 0.0001) were observed between mapping sites 2 and 1, and 3 and 2. The negative value calculated between sites 2 and 1 reflected activation moving toward the os from accessory pathways located at the left border of the posterior septum. For patients in group III with left posterior pathways, no significant changes in absolute interelectrode conduction times or direction of activation along the coronary sinus were observed. Activation proceeded predominantly toward the os, as indicated by the negative conduction times.

Significant changes in directional conduction times measured during maximal ventricular preexcitation (Figure 7) distinguished group I from II at the same mapping sites that differentiated these groups during

orthodromic supraventricular tachycardia. However, in contrast to the data during orthodromic tachycardia, interelectrode conduction times were all positive, and the significant differences between the mapping sites in these groups reflected a large increase in conduction time rather than a directional change in conduction. The positive values indicate that conduction proceeded from the os to the left free wall. In group I, the most rapid conduction bridged the posterior septum and left posterior free wall (between mapping sites 3 and 2). In contrast, the most rapid conduction occurred within the septum between mapping sites 2 and 1 in Group II. In Group III, interelectrode conduction times were negative and indicated activation toward the os.

Predictive power of directional conduction times: Traditional determinants of accessory pathway location rely on identification of sites at which measurements of the ventriculoatrial interval during orthodromic supraventricular tachycardia and the delta (QRS complex)-ventricular interval during maximal preexcitation are the shortest. Based on the coronary sinus mapping schema (Figure 1), accessory pathways were confined to the posterior septum when the earliest anterograde and ret-
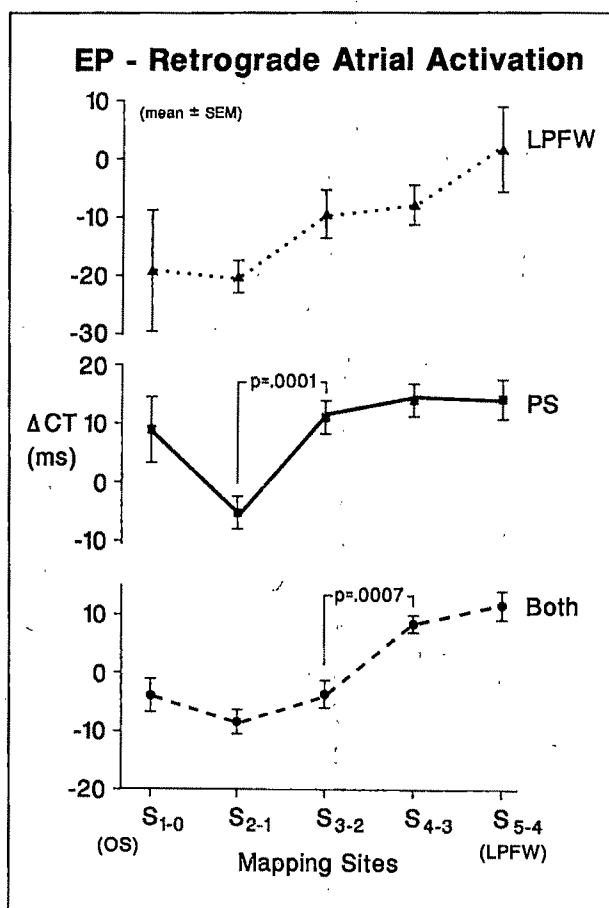
FIGURE 6. Within-group analysis of directional conduction times (ΔCT) during orthodromic supraventricular tachycardia. Data from each group are plotted on separate y axes. Significant differences in directional conduction times were observed among combined and posterior septal (PS) groups. These differences represent directional changes in conduction. Other abbreviations as in Figure 4.
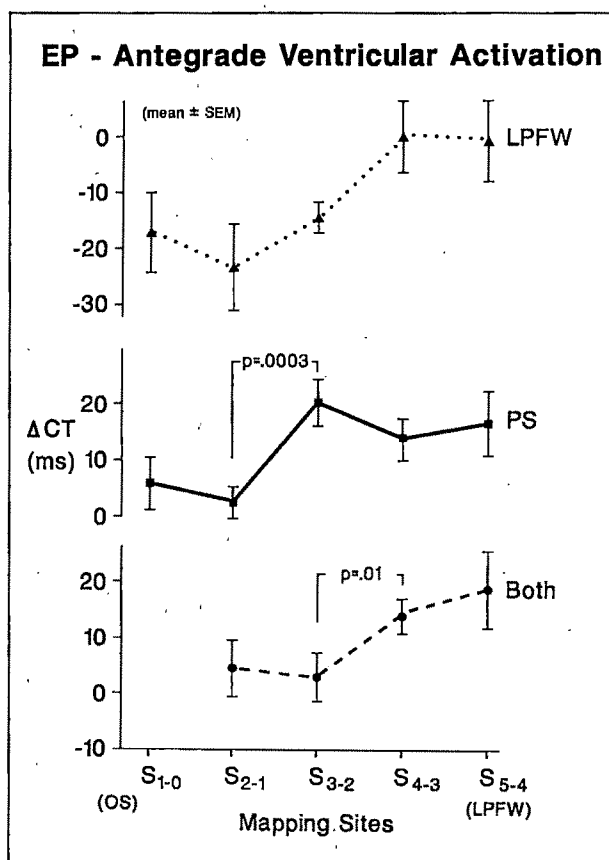
FIGURE 7. Within-group analysis of directional conduction times (ΔCT) during maximal ventricular preexcitation. Data from each patient group are plotted on separate y axes. Significant differences in directional conduction times were observed for combined and posterior septal (PS) groups at identical sites seen during orthodromic supraventricular tachycardia. These differences reflect sudden change in conduction times between adjacent electrode sites. Other abbreviations as in Figure 4.

rograde activation occurred at site 0, 1 or 2. The left posterior free wall began at site 3. Both regions were involved when the earliest activation bridged sites 2 and 3. With the use of this traditional approach, only 7 of 21 patients (33%) who needed dissection of both anatomic regions would have been classified correctly. A broad band of tissue that activated simultaneously or tangentially early sites of activation traversing both anatomic regions was observed in 5 and 4 of these 7 patients, respectively. Of the remaining 14 pathways, 7 would have been localized to the posterior septum and 7 to the left posterior free wall.

Analysis of logistic regression models demonstrated that the anterograde and retrograde directional conduction times between mapping sites 3 and 2 (p = 0.004), and the change in these values between mapping sites 3 and 2, and 2 and 1 (p = 0.003, anterograde; and p = 0.05, retrograde) were powerful univariate predictors of accessory pathways that bridged both zones. In a multiple regression model, both predictors remained significant for anterograde data (sensitivity 87% and specificity 90%), whereas only the directional conduction time measured between mapping sites 3 and 2 remained significant for retrograde data (sensitivity 80% and specificity 67%). The incorporation of both anterograde and retrograde predictors in the model conferred no additional significance over the anterograde directional conduction time measured between sites 3 and 2 alone in correctly identifying accessory pathways bridging the posterior septum and the left posterior free wall.

DISCUSSION

Traditional determinants of accessory pathway location have been based on the earliest atrial and ventricular activation during orthodromic supraventricular tachycardia and maximal ventricular preexcitation, respectively.[4,5] With this approach, the locations of the accessory pathways in 14 of 21 patients in group I found at surgery to bridge the posterior septum and the left posterior free wall were misclassified as either within the posterior septum or on the left posterior wall.

This study was performed to determine the extent to which a new directional measure of conduction time between adjacent coronary sinus mapping sites improves the identification of accessory pathways that bridge these anatomic regions. Major features of this study are inclusion of patients with posterior septal (group II) and left posterior (group III) pathways as controls, determination of the locations of the accessory pathways based on comprehensive catheter mapping of the coronary sinus and computer-assisted mapping of the atrioventricular groove intraoperatively, and successful surgical dissection of all accessory pathway tissue. Analysis of directional conduction times identified significant differences in both the rate and direction of conduction that were unique to accessory pathways that bridged the posterior septum and the left posterior free wall, and distinguished them from pathways confined to either region alone.

For patients in groups I and II, observed differences showed a directional change in conduction during or-

thodromic tachycardia compared with a large increase in conduction time without an associated directional change at the same mapping sites during maximal preexcitation. In group II, 2 sites of early atrial activation (S_0 and S_2) were observed. Although earliest activation occurred at the os (S_0), the single negative value at S_{2-1} (bracketed by positive conduction times) shows a second "point source" at S_2 from which activation spread both toward and away from the os of the coronary sinus. This pattern contrasts with that of retrograde atrial activation observed in group I, where negative directional conduction times indicating conduction toward the os extended over a broader band of tissue (S_{3-2} to S_{1-0}), and activation away from the os extended laterally from mapping sites S_{4-3}.

Site-specific sudden changes in interelectrode conduction times characterized each group. For group I, rapid conduction occurred between mapping sites 3 and 2 with a sudden decrease in conduction over the left posterior free wall. In contrast, for Group II patients, conduction was most rapid within the septum but slowed markedly between mapping sites 3 and 2. The number of patients in group III was small, and statistically significant within-group changes in adjacent directional conduction times were not observed. However, anterograde and retrograde directional conduction times demonstrated uniform conduction toward the os from lateral mapping sites with the most rapid conduction measured between the lateral and left posterior sites, distinguishing Group III from I.

The anatomy of the posterior septum is pertinent to the coronary sinus mapping scheme used in this study. Davis et al[15] reported the dimensions of the posterior septum based on analysis of 48 cadaver hearts. The mean distance from the coronary sinus os to the left margin of the posterior septum was 2.3 ± 0.4 cm. This distance closely approximates the 2.5 to 3.0 cm distance from the os to site 3, which defined the left posterior free wall in the present study. These dimensions are also in keeping with preliminary findings from patients who needed a left ventricular approach to ablate accessory pathways thought to be within the posterior septum. Features of pathways in this region included detection of pathway potentials along the tricuspid annulus during anterograde conduction and 2.5 to 3.0 cm from the os during retrograde conduction.[16]

Results are based on retrospective analysis of catheter maps from patients found at surgery to have accessory pathways confined to the posterior septum or left posterior free wall, or to bridge both anatomic regions. The jackknife procedure was used in the regression models to eliminate bias introduced by use of the test data set to predict the likelihood that directional measures of conduction time would distinguish pathways bridging the posterior septum and left posterior free wall. Univariate predictors were so powerful that they had little or no additive value in combination, a result that underscores the need to perform a prospective study with larger numbers of patients to assess the true power of the directional conduction times to identify accessory pathways that bridge the posterior septum and

left posterior free wall in patients with Wolff-Parkinson-White syndrome referred for catheter or surgical ablation.

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Recordings from the Slow Zone of Reentry During Burst Pacing Versus Programmed Premature Stimulation for Initiation of Reentrant Ventricular Tachycardia in Patients with Coronary Artery Disease

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Programmed premature stimulation and burst pacing were compared for initiation of ventricular tachycardia (VT) in 16 patients with inducible sustained monomorphic VT. In all patients VT could be induced by programmed stimulation with 2 or 3 extrastimuli. On the other hand, initiation of VT by burst pacing was dependent on the length of the train; only 2 to 4 of the 11 trains tested could induce VT in any single patient. Recordings obtained from the slow zone of reentry showed that programmed premature stimulation that induced VT resulted in a critical degree of conduction delay as revealed by lengthening of local fractionated electrograms spanning 70 to 100% of the diastolic interval. Similarly, the last beat of a burst pacing train that induced VT was always followed by a similar degree of local conduction delay, whereas trains that failed to induce VT were followed by a lesser delay. It is concluded that although programmed stimulation with up to 3 extrastimuli was consistently successful in inducing VT, burst pacing succeeded in only 26% of the trials and was dependent on the length of the train, which varied from one patient to the other. Similar to what was shown previously in the experimental model of reentrant VT, burst pacing could initiate, conceal, terminate, and reinitiate reentry depending on the length of the train.

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Initiation of reentrant tachycardia by trains of fast cardiac stimulation, i.e., burst pacing or by programmed premature stimulation, or both, has been described in experimental[1-3] as well as in clinical settings.[4-6] Both programmed premature stimulation and burst pacing have been used to initiate reentrant ventricular tachycardia (VT) in the canine postinfarction model.[3] The mechanism of initiation of reentrant VT by burst pacing versus programmed premature stimulation in this model has been previously described.[7] It was shown that initiation of reentry by burst pacing depends not only on the cycle length of stimulation, but also, critically, on the number of beats in the paced run. There are no similar data available in clinical examples of reentrant VT. This study investigates this subject in patients with inducible sustained monomorphic VT by using left ventricular endocardial electrode catheter recordings from the slow zone of reentry.

METHODS

Study patients: Sixteen patients (14 men and 2 women) with history of coronary artery disease and spontaneous sustained monomorphic VT (10 patients) or nonsustained VT (6 patients) were included in the study. By definition all patients had inducible sustained monomorphic VT at electrophysiologic study.

Electrophysiologic study: After informed consent was obtained, multipolar electrode catheters were inserted percutaneously into femoral veins and a femoral artery. Catheters were positioned at the right ventricular apex or outflow tract, His bundle position and in the left ventricle (in 6 patients). Three surface electrocardiographic leads were recorded simultaneously with intracardiac electrograms at a paper speed of 100 to 150 mm/s on an Electronics for Medicine VR-12 chart recorder. Intracardiac electrograms were filtered at 30 to 500 Hz and recorded at a gain of 1 to 3 cm/mV. Full standard 12-lead electrocardiograms were recorded at a paper speed of 25 mm/s (Marquette, Inc.) during stable-induced VT and ventricular pacing.

Stimulation protocol: Ventricular stimuli at twice diastolic threshold of 2 ms were delivered by a programmable stimulator (DTU-101 MVA, Bloom Associates).

Programmed premature stimulation: During regular ventricular pacing (S_1) at cycle lengths of 400, 500 and 600 ms, single (S_2), double (S_2, S_3) or triple (S_2, S_3, S_4) premature stimuli were introduced. A single premature stimulus (S_2) was introduced late in diastole,

TABLE I Programmed Premature Stimulation and Burst Pacing Protocols in 16 Patients

Pt. No.	Age (yr) & Sex	Heart Disease	Programmed Premature Stimulation	Burst Pacing*
1	64 M	IWMI	$S_1 S_2 S_3$	4, 5, 9 (4, 5, 8)
2	72 M	IWMI	$S_1 S_2 S_3 S_4$	5, 8, 11
3	74 M	AWMI, AN	$S_1 S_2 S_3$	4, 5, 8
4	55 M	IWMI	$S_1 S_2 S_3 S_4$	5, 6, 9 (5, 7, 10)
5	60 M	I + AWMI	$S_1 S_2 S_3$	4, 6, 10 (4, 5, 9)
6	59 F	NQMI	$S_1 S_2 S_3$	4, 7, 10, 11
7	48 M	IWMI, AN	$S_1 S_2 S_3 S_4$	5, 8
8	55 M	AWMI	$S_1 S_2 S_3 S_4$	5, 6, 10 (5, 6, 9)
9	62 F	NQMI	$S_1 S_2 S_3$	4, 7, 11
10	58 M	AWMI	$S_1 S_2 S_3$	5, 9, 10
11†	61 M	AWMI	$S_1 S_2 S_3 S_4$	5, 10 (5, 6, 10)
12†	63 M	IWMI	$S_1 S_2 S_3$	4, 8
13†	59 M	I + AWMI	$S_1 S_2 S_3 S_4$	4, 9, 11 (4, 8, 9, 11)
14†	65 M	AWMI	$S_1 S_2 S_3$	4, 8
15†	72 M	AWMI	$S_1 S_2 S_3$	4, 7, 9
16†	66 M	I + AWMI	$S_1 S_2 S_3 S_4$	5, 9, 10

*This column shows the number of beats in paced trains that induced ventricular tachycardia. Numbers between brackets are the results on repeating the burst pacing protocol when different from control.
†Patients had recordings from the slow zone of the reentrant circuit.
AN = aneurysm; AWMI = anterior wall myocardial infarction; I = inferior; IWMI = inferior wall myocardial infarction; NQMI = non-Q-wave myocardial infarction.

and the coupling interval was gradually shortened until VT was initiated or until the effective refractory period of the right ventricular site was reached. If S_2 failed to initiate VT, its coupling was fixed at an interval 10 ms longer than the refractory period and an S_3 was introduced at gradually shorter coupling intervals until S_3 either provoked a response or reached refractoriness. If the latter occurred, then S_3 coupling was fixed at an interval 10 ms longer than the refractory period and an S_4 was introduced in the same manner until VT was initiated.

Burst pacing: Burst pacing was applied during sinus rhythm in the form of trains of 2 to 12 paced beats at a fixed cycle length, 10 ms longer than the effective refractory period of S_2 (i.e., at a cycle length equal to S_1–S_2 coupling interval during programmed premature stimulation). This assured 1:1 capture during ventricular pacing. Each paced train was programmed to start in the late diastolic interval at a cycle length of 50 to 100 ms shorter than the sinus cycle length. The complete burst pacing protocol was applied only at a single cycle length. Both programmed premature stimulation and burst pacing protocols were applied twice in each patient.

Ventricular mapping of the slow zone of the reentrant circuit: Endocardial mapping was performed in 6 patients with a 6Fr quadripolar catheter with 1 cm interelectrode distance (USCI). Catheter positions were verified by fluoroscopy in 2 planes and designated by the endocardial coordinates of Josephson et al.[8] Bipolar electrograms were recorded from the distal electrode pair and the proximal electrode pair of the mapping catheter during sinus rhythm. Fractionated electrograms were defined as those having a duration >60 ms and multiple rapid low amplitude (<0.05 mV) deflections.[8,9] VT was then induced and mapping was performed to localize a site of mid-diastolic or pandiastolic fractionated electrical activity during the tachycardia. This site was identified as the slow zone of the reentrant

circuit. This was further confirmed by pace mapping from the site.[9,10] The morphology of paced QRS in all 12-lead electrocardiograms were compared with that of spontaneous or induced VT, or both. In 5 of the 6 patients direct-current high-energy shocks were delivered to this site (2 to 4 shocks at 200 to 400 J) to ablate the reentrant circuit.[11] In all 5 patients VT was no longer inducible during the initial electrophysiologic study, nor at a follow-up study 2 weeks later.

RESULTS

In 6 of the 16 patients, VT could be induced by 2 premature stimuli. In the remaining 10 patients, 3 premature stimuli were required. In all patients, VT could also be induced by burst pacing. However, successful induction was dependent on the number of stimuli in a paced train. Only 2 to 4 of the 11 trains tested could induce VT in any single patient. For the entire group only 26% of all trains tested succeeded in inducing VT. The length of the trains that induced VT varied from one patient to the other. The results of programmed premature stimulation were reproducible in all patients, whereas the burst pacing protocol was only reproducible in 10 of 16 patients. Table 1 summarizes the results of the stimulation protocol in all 16 patients.

Figure 1 illustrates electrocardiographic recordings from 1 of the patients (no. 6). Sustained monomorphic VT could be induced by 2 premature stimuli and by burst pacing. Figure 1A shows that during S_1 stimulation at a cycle length of 400 ms, S_2 and S_3 stimuli were introduced at coupling intervals of 260 and 220 ms, respectively, and initiated a monomorphic VT at a cycle length of 420 to 430 ms.

Burst pacing at a cycle length of 260 ms could initiate VT only with paced trains of 4 and 9 stimuli, but not with paced trains of 2, 3, 5, 6, 7, 8, 10, 11 or 12 beats (Figure 1B).

Figures 2 and 3 illustrate recordings from the slow zone of the reentrant circuit from patient 14. Sustained

monomorphic VT could be induced by 2 premature stimuli as well as by burst pacing trains of 4 and 8 stimuli. Figure 2 shows that fractionated electrograms extending into the diastolic interval were recorded from left ventricular septal sites during sinus rhythm and during regular ventricular stimulation at a cycle length of 500 ms. The duration of the local electrograms was 290 to 300 ms during S_1 pacing. The introduction of a single premature stimulus (S_2) at a coupling interval of 280 ms (10 ms longer than local refractoriness) only resulted in slight increase of the duration of local electrograms to 310 ms (Figure 2A). The duration of the fractionated electrograms lengthened to 390 ms with the introduction of a second premature stimulus (S_3) at a cycle length of 250 ms but VT could not be induced (Figure 2B). Shortening of the S_2-S_3 interval to 220 ms resulted in further lengthening of the duration of the fractionated electrograms to 420 ms and the initiation of sustained monomorphic VT at a cycle length of 430 to 440 ms (Figure 2C). During VT fractionated activity spanned the diastolic interval.

Figure 3A illustrates the induction of VT by a burst pacing train of 4 stimuli. The last beat of the paced train resulted in lengthening of the duration of the fractionated electrograms to 420 ms, similar to that pro-

duced by the introduction of 2 premature stimuli shown in Figure 2C. The last beat of an 8-stimuli paced train was also associated with a similar degree of lengthening of the fractionated electrograms and initiation of VT (not shown in the figure). By contrast, the last beat of paced trains that failed to induce VT was associated with lesser degree of conduction delay. Figure 3, B and C, shows that the last beat of 5- and 7-stimuli paced trains was associated with a duration of 250 and 270 ms, respectively, of the fractionated electrograms. In all 6 patients in whom recordings from the slow zone of the reentrant circuit were obtained the premature stimulus that induced VT (S_3 or S_4) resulted in critical lengthening of the local fractionated electrograms. The duration of the fractionated electrograms associated with VT induction ranged from 380 to 520 ms (mean 420 ± 36) and spanned 70 to 100% of the diastolic interval. The duration of fractionated electrograms associated with the last beat of paced trains that induced VT varied by 20 ms or less from those induced by successful premature stimulation.

The programmed premature stimulation protocol was reproducible in all patients. However, the burst pacing protocol was not reproducible in 6 of 16 patients. Figure 4 illustrates the nonreproducibility of the burst

FIGURE 1. Electrocardiographic recordings from patient 6 showing the induction of ventricular tachycardia by 2 premature stimuli *(A)* and burst pacing (BP) trains of 4 and 9 beats *(B).* All other burst pacing trains failed to induce ventricular tachycardia.
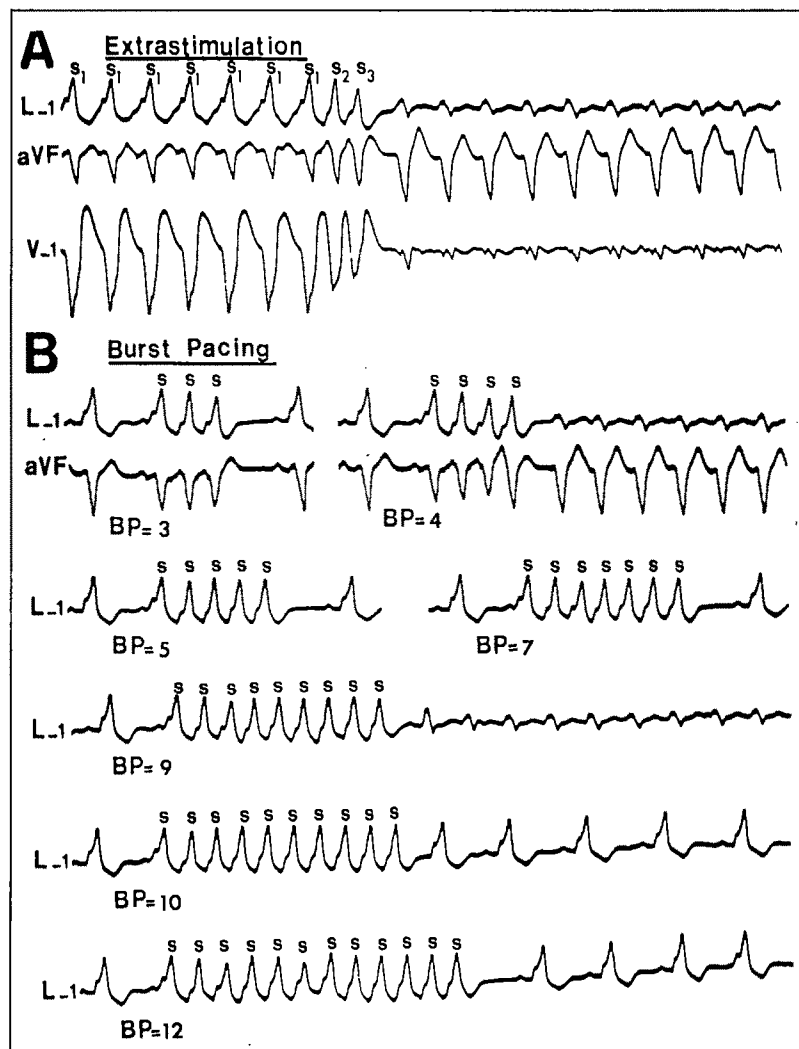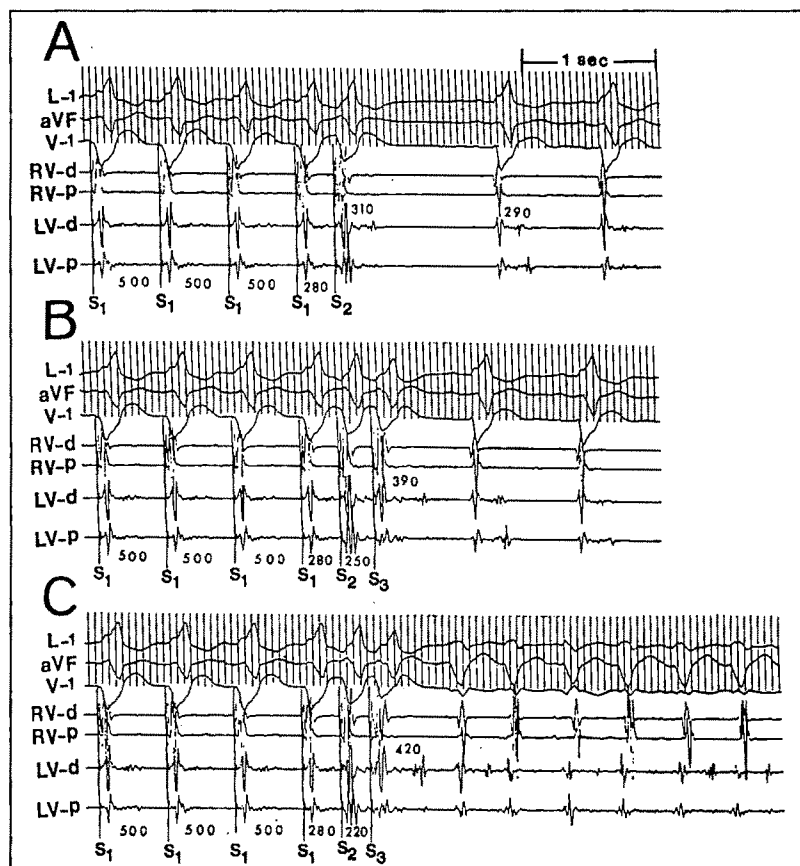
FIGURE 2. Recordings from the slow zone of the reentrant circuit from patient 14 during the induction of ventricular tachycardia by programmed premature stimulation. In each recording the *upper set of numbers* represent the duration of local fractionated electrograms in milliseconds and the *lower set of numbers,* the cycle length of stimulation. LV-p and LVd = proximal and distal recordings, respectively, from left ventricular septal sites; RV-p and RV-d = proximal and distal recordings, respectively, from right ventricular septal sites. See text for details.
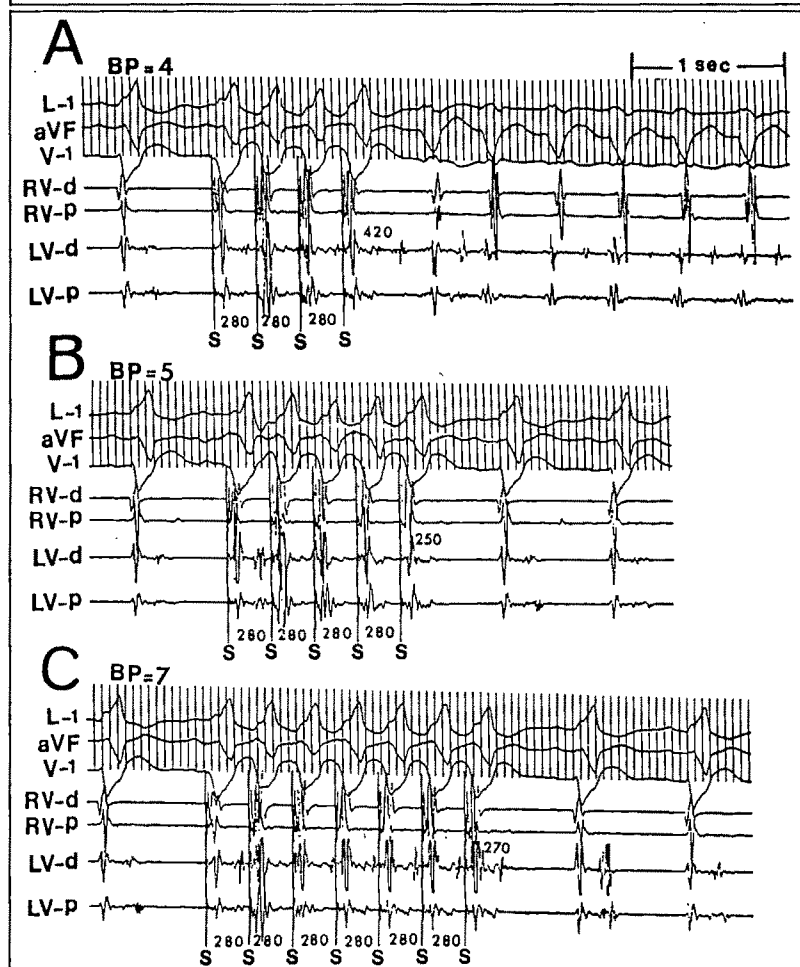
FIGURE 3. Recordings from the slow zone of the reentrant circuit from patient 14 during burst pacing (BP). In each recording the *upper set of numbers* represent the duration of local fractionated electrograms in milliseconds and *the lower set of numbers,* the cycle length of stimulation. Recordings are from the same sites as in Figure 2. See text for details.

pacing protocol in 1 of the patients. The figure shows that 2 consecutive 6-beat trains at a cycle length of 280 ms and with a constant coupling interval of the first paced beat failed to induce VT during the first trial (panel A) but succeeded in the second trial (panel B). The duration of local activity associated with successive paced beats is represented by the length of the arrows and labeled in milliseconds at the bottom of each recording. In panel A, the first 4 paced beats resulted in gradual lengthening of the duration of local activation (from 170 to 250 ms). This was followed by abrupt shortening of the duration of local activation of the fifth as well as the sixth and last beat (175 and 170 ms respectively). The latter was not followed by VT. However, in panel B, similar lengthening of the duration of fractionated electrograms following S_1 to S_4 was observed followed by abrupt shortening of activation of S_5 (from 240 to 175 ms). However, S_6, this time, was associated with a markedly prolonged fractionated electrogram of 360 ms that bridged the entire diastolic interval and initiated a monomorphic VT. During VT diastolic bridging by fractionated activation was also present. The changes in the duration of local fractionated electrograms, as shown in Figure 4, suggest that burst pacing trains resulted in a Wenckebach-like pattern of local conduction delay and that VT was induced only when the train was terminated with the beat associated with the longest conduction delay.

DISCUSSION

The incidence of inducible ventricular tachyarrhythmias varies directly with the number of extrastimuli applied during basic ventricular pacing both in patients with spontaneous sustained and nonsustained VT. In patients with spontaneous sustained VT, the probability of inducing sustained monomorphic VT ranged from 22 to 33% (mean 27%) with 1 extrastimulus, from 47 to 73% (mean 66%) with 2 extrastimuli, and from 75 to 94% (mean 88%) with 3 extrastimuli.[12-16] Similar findings were reported in patients with spontaneous nonsustained VT. Four studies that utilized a similar stimulation protocol reported their data according to the number of extrastimuli required for induction.[16-19] The fraction of patients who had sustained monomorphic VT induced by one extrastimulus was low (0 to 3%), increased substantially with 2 extrastimuli (9 to 24%), and showed further increase with 3 extrastimuli (21 to 39%).

Burst pacing was used by several investigators to induce ventricular tachyarrhythmias in patients with spontaneous nonsustained VT. The additional yield of this mode of stimulation above the use of 2 extrastimuli ranged from 3%[20,21] to 11%.[12] Similar results were reported in patients with spontaneous sustained VT.[12,19,22,23] However, burst pacing may have no advantage over the use of 3 extrastimuli.[21] A protocol using an abrupt short-long sequence of the basic drive before
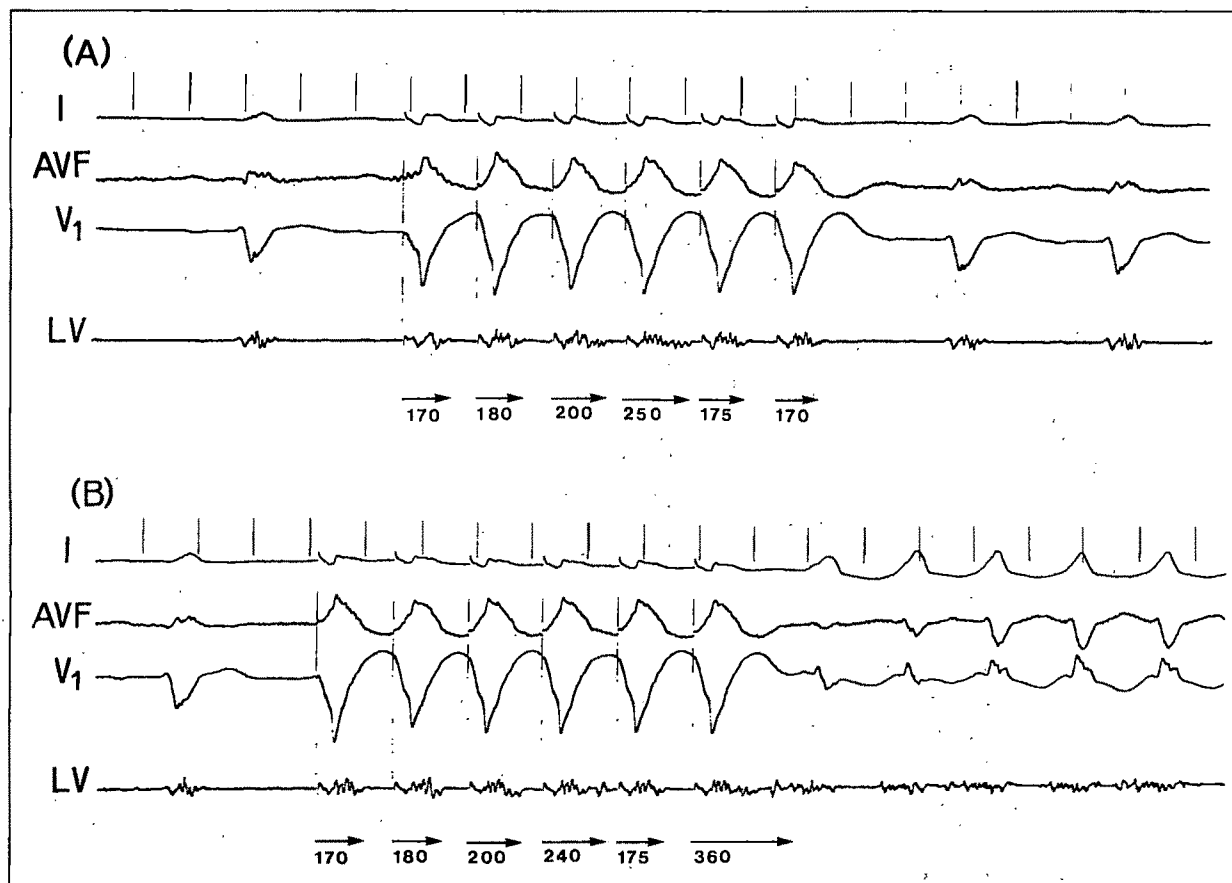
FIGURE 4. Recordings from the slow zone of the reentrant circuit from patient 11 during 2 consecutive burst pacing trains of 6 beats. The first train failed to induce ventricular tachycardia, whereas the second train did. *Numbers* represent the duration of local fractionated electrograms. See text for details.

FIGURE 5. Diagrammatic representation of cardiac activation patterns during the induction of ventricular tachycardia by trains of burst pacing (BP). See text for details.

gressively longer arcs of functional conduction block (represented by heavy solid lines) and slower circulating wave fronts (represented by undulating lines). If the slow wave front of S_4 reaches the distal side of the arc of block, after a critical degree of conduction delay, it could reexcite myocardial zones on the proximal side of the arc after expiration of refractoriness to initiate circus movement reentry. For manifest reentry to take place, the paced run should be terminated after the beat that resulted in a critical degree of conduction delay. If rapid pacing was extended past this beat (as in Figure 5, panel B) reentrant activation could be confined (concealed) to the zone of early reexcitation by the next paced beat S_5. This beat could also advance rapidly to the slow zone of the reentrant circuit resulting in conduction block and interruption of reentrant excitation. Termination of a paced train after this beat would not result in reentry. If the paced train is continued past the beat that interrupted reentry, e.g. S_6, S_7, and so forth, a new sequence of ventricular activation patterns characterized by progressively longer arcs of conduction block or slower conduction, or both, will again develop.

Study limitations: The present study investigated only burst pacing trains at a single cycle length. In the experimental model, changing the cycle length of the paced trains could also influence the length of the trains that successfully induced reentry.[3,7] The site of the slow zone of the reentrant circuit was validated both by pace mapping as well as by the successful ablation of reentry when direct-current shock was applied to the site. However, the interpretation of changes in the duration of local fractionated electrograms with programmed stimulation should be viewed carefully. On one hand, the changes shown in the present study were remarkably similar to those obtained from a composite electrode recording from the site of reentrant circuit in the experimental model.[3] Detailed activation maps in the same model lend credence to the interpretation of composite electrode recordings.[7] On the other hand, the duration of fractionated electrograms only reflects the degree of conduction delay in the reentrant circuit. Details of other prerequisites for successful circus movement reentry, e.g., the presence and length of arcs of functional conduction block[26] cannot be obtained from the current recording technique. Finally, the conclusions regarding burst pacing are only applicable to VT secondary to a reentrant mechanism. Rapid pacing was shown to be successful in inducing triggered rhythms due to delayed afterdepolarizations in the experimental setting.[27] The presence of such rhythms in the clinical setting is difficult to document.

the introduction of ≥1 extrastimuli was reported to initiate sustained VT in patients not otherwise inducible with conventional protocols.[24] However, when the efficacy of such a technique was compared with the use of triple extrastimuli, no significant difference was found.[25]

Mechanism of induction of reentrant tachycardia by burst pacing: The present clinical observations are similar to those described in the postinfarction canine model of reentrant excitation when composite electrode recordings from the ischemic zone were analyzed.[2] Isochronal mapping of reentrant activation in this model[7] showed the following mechanism for initiation of reentry by burst pacing (Figure 5). Figure 5 shows that a 4-beat paced train induced a reentrant VT (panel A), whereas a 6-beat train failed to induce reentry (panel B). In the first case, the 4 successive paced beats applied at a critically short cycle length resulted in pro-

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Radiation Exposure to Patients and Medical Personnel During Radiofrequency Catheter Ablation for Supraventricular Tachycardia

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Radiofrequency catheter ablation is an effective alternative to medical therapy for patients with supraventricular arrhythmias. The purpose of this study was to determine the risks to the patient and to medical personnel due to radiation exposure from fluoroscopy during radiofrequency ablation of supraventricular tachycardia. One hundred eight consecutive patients with Wolff-Parkinson-White syndrome or atrioventricular nodal reentry who underwent the ablation procedure were studied. The ablation procedure was successful in 95% of the patients studied. Preexcitation or supraventricular tachycardia recurred in 5% of the patients during a mean follow-up of 9 ± 4 months. The mean fluoroscopy time was 50 ± 31 minutes. An anthropomorphic radiologic phantom was used to determine organ exposure and the effective dose equivalents for the patient and medical personnel. The patient's effective dose equivalent during a representative ablation procedure was 1.7 rems, which is comparable to other invasive cardiovascular procedures. The risk of inducing a fatal cancer from this exposure is 1 chance in 745, which is 1% of the spontaneous risk. The risk of a serious birth defect is 1 chance in 80,000, which is 0.1% of the current incidence of serious birth defects in the United States. The cardiologist who receives the highest exposure among medical personnel, would incur 1.8 mrems per case or 450 mrems per year if 250 procedures were performed. This exposure is 9% of the recommended annual limit. These results demonstrate the efficacy of radiofrequency energy ablation of supraventricular tachycardia and confirm that radiation exposure to patients and medical personnel is within established guidelines.

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The remarkable success of arrhythmia ablation procedures has encouraged physicians to refer children and adults with supraventricular tachycardia for electrophysiologic intervention as the first line of therapy.[1-10] Moreover, there is a growing sentiment that arrhythmia ablation procedures are preferred to effective medical therapy because of the potential risks, expense and inconvenience associated with the long-term use of antiarrhythmic drugs. Patients with ventricular preexcitation may also be referred for ablation of an accessory pathway even if they have never experienced symptoms. The enthusiasm for arrhythmia ablation procedures must be tempered by the recognition that these procedures do have associated risks. Although the immediate risks of cardiac perforation, vascular injury, valvular damage, stroke or iatrogenic heart block are extremely low, it is imperative to determine that arrhythmia ablation procedures, which often require the prolonged use of fluoroscopy, do not subject patients to excessive levels of radiation. The purpose of this study was to determine the risks imposed by radiation exposure to the patient and to the medical personnel who perform these procedures, and to identify techniques that reduce this exposure.

METHODS

Patients: One hundred eight consecutive patients with the Wolff-Parkinson-White syndrome or atrioventricular (AV) nodal reentry were studied. The arrhythmia ablation protocol was approved by the Human Studies Committee and informed written consent was obtained from each patient. During the electrophysiologic study intracardiac recordings were obtained from the right atrium, the coronary sinus, the AV junction and the right ventricle. A Seimens Cordoskop C x-ray unit was used for fluoroscopic imaging, and the field of image was collimated to the smallest area required to position catheters. For patients with AV nodal reentry or accessory pathways that could be ablated from the right side of the heart, the right atrial catheter was exchanged for a 7Fr deflectable ablation catheter with a 4 mm distal electrode. For patients with accessory pathways at left free wall or left paraseptal sites, the ablation catheter was inserted in a femoral artery and positioned in the left ventricle.

In patients with AV nodal reentry the objective was to eliminate or modify the slow AV nodal pathway preferentially or to modify the fast pathway if the first objective was not achieved. Slow-pathway modifications were performed by applying radiofrequency energy at the site of presumed slow-pathway potentials recorded

along the tricuspid annulus between the His-Bundle and the os of the coronary sinus.[8-10] The therapeutic end point was complete elimination of dual AV nodal physiology or the inability to induce repetitive AV nodal reentrant beats despite the persistence of discontinuous AV nodal conduction curves.[10] When the slow-pathway could not be modified, radiofrequency energy was used to eliminate or modify retrograde AV nodal conduction using methods previously reported.[3] Accessory pathways were ablated by positioning the tip of the ablation catheter at the ventricular insertion of the accessory pathway. The end point of treatment was elimination of anterograde and retrograde conduction through the accessory pathway. Patients were observed for 1 hour after these end points were achieved. Programmed stimulation was then repeated in the resting state and during an infusion of isoproterenol to confirm that the procedure was successful.

Tissue ablation was performed with a continuous-wave 500 KHz radiofrequency current generated by an electrosurgical unit (Bicap 5005, Microinvasive, Inc., Watertown, Massachusetts) that was modified to increase its voltage output. A control unit (Mansfield Scientific, Watertown, Massachusetts) was used to select the duration and voltage of the current and to monitor voltage, current and impedance. Twenty-five to 35 W were applied for approximately 60 seconds at the site selected for tissue destruction.

Radiation exposure: Radiation measurements were obtained during fluoroscopy of an anthropomorphic radiologic phantom (Radiologic Support Devices, Long Beach, California). The phantom is a model of the human chest corresponding to a patient 5 feet 9 inches in height and 73.4 kg in weight. The model extends from the neck to below the diaphragms and contains a synthetic heart, lungs, pulmonary vasculature, and skeletal structures that are radiographically equivalent to human tissues. The radiation exposure measurements were obtained with a Radcal Corporation (Monrovia, California) model 2025 x-ray monitor using a Radcal Corporation model 20 X 5-3 electrometer/ion chamber for the primary beam and a model 20 X 5-1800 electrometer/ion chamber for secondary radiation measurements.

The entrance exposure rates were obtained for posteroanterior, right anterior oblique and left anterior oblique projections that are frequently used during the ablation procedure. The focal skin distance for each of the views was approximately 24 inches. Radiation levels due to secondary radiation, primarily scattered from the irradiated phantom, were measured at selected locations for each of the 3 commonly used projections. These measurements were recorded at the position occupied by the physician performing the procedure approximately 30 inches from the chest, at the electrophysiologic monitoring station approximately 8 feet from the chest where programmed stimulation is performed, and at the position occupied by the nurse (8 feet from the chest). The dose rates were also determined for areas near the primary beam but on the exit side of the beam (anterior chest of patient) where the physician's hands may be positioned in order to manipulate a catheter inserted into the subclavian vein.

TABLE I Characteristics of Patients Studied		
	WPW Syndrome	AV Nodal Reentry
No of pts.	64	44
Male/female	42/22	15/29
Age (yr)		
Mean	36 ± 19	43 ± 17
Range	12–75	12–77
Successful procedure	59 (90%)	44 (100%)
Follow-up (mos)	9 ± 4	8 ± 4
Recurrence	3 (5%)	2 (5%)
AV = atrioventricular; WPW = Wolff-Parkinson-White.		

Risk projections: Radiation measurements obtained from the entrance point of the primary beam were used to compute organ exposure for the patient.[11] Secondary beam measurements were used to compute organ exposure for the physician and other medical personnel who performed the procedure. The effective dose equivalent was obtained by weighting each organ dose by its relative susceptibility of harm due to radiation and then by summing over the organs of the body. The computed quantity is projected to equal the uniform radiation dose to the whole body that imparts the same health risk as the actual nonuniform exposure. The dose to the heart was not included in this calculation because it is highly resistent to radiation-induced cancer. The 1990 National Research Report on the biological effects of ionizing radiation was used to estimate the somatic risks of low-level ionizing radiation.[12] These projections assume a dose-response relation that is linear for acute doses <10 rems. The risk of developing a fatal cancer induced by radiation was calculated and then compared with the risk of dying from a cancer that is unrelated to radiation exposure.

RESULTS

Patients studied: The characteristics of the 108 patients who underwent radiofrequency ablation procedures are listed in Table I. There were 64 patients with Wolff-Parkinson-White syndrome and 44 patients with AV nodal reentry. Fifty-seven patients were men and 51 were women (age range 12 to 77 years). In patients with Wolff-Parkinson-White syndrome the accessory pathway was in the left free wall in 48 patients, the posterior septum/posterior paraseptal region in 11 patients, and the anterior septum/right anterior paraseptal region in 3 patients, and the right free wall in 2 patients. The accessory pathway was concealed in 19 patients (30%). The ablation procedure was judged to be successful in 95% of all patients studied, in 92% of the patients with Wolff-Parkinson-White syndrome, and in all of the patients with AV nodal reentry. During a mean follow-up of 9 ± 4 months (range 1 to 17) in patients with Wolff-Parkinson-White syndrome, ventricular preexcitation or supraventricular tachycardia recurred in 3 patients (5%). Two patients (5%) have had a recurrence of AV nodal reentry over a mean follow-up of 8 ± 4 months (range 1 to 17).

Fluoroscopy time: The mean fluoroscopy time for all 108 patients was 50 ± 31 minutes. The mean fluoroscopy time for patients with Wolff-Parkinson-White syn-

TABLE II Primary Beam Measurements			
X-Ray Projection	kV	mA	Entrance Exposure (roentgens/min)
Posteroanterior	66	4.4	1.6
Right anterior oblique	70	4.8	2.0
Left anterior oblique	70	5.2	2.2
kV = kilovolts; mA = milliamperes.			

TABLE III Secondary Beam Measurements (mrem/hour)			
	X-Ray Projection		
Subject	PA	RAO	LAO
Cardiologist (femoral position)			
Beam open: no shield	47	21	80
Cardiologist (subclavian position)			
Beam open: no shield	70	30	210
Beam collimated: no shield	36	11	100
Beam open: shield used	2	7	5
Monitoring personnel			
Beam open: no shield	15	9	30
Nurse			
Beam open: no shield	8	5	4
LAO = left anterior oblique; PA = posteroanterior; RAO = right anterior oblique.			

drome was 54 ± 37 minutes (range 11 to 180) and for patients with AV nodal reentry, 45 ± 18 minutes (range 15 to 90) (p = not significant). The fluoroscopy time was significantly (p <0.05) shorter for the last 54 procedures (43 ± 21 minutes) than for the first 54 procedures (44 ± 22 minutes). Figure 1 compares the proportions of patients with relatively brief, intermediate and prolonged fluoroscopy exposure. The fluoroscopy time was ≤30 minutes in 28% of patients, 31 to 60 minutes in 49%, 61 to 90 minutes in 16%, and >90 minutes in only 7% of the patients studied.

Radiation measurements: The entrance exposure rates obtained from the primary beam (without collimation) for the 3 projections that are frequently used to position catheters are listed in Table II. By collimating the field of image (Figure 2), the radiation exposure to the patient and to the medical personnel was reduced by 40%. This practice, which was adhered to during the ablation procedure, was taken into consideration when organ doses were calculated.

Radiation levels due to secondary radiation, which is primarily due to scatter, are listed in Table III. As expected, the exposure is greatest for the physician who manipulates the catheter. These recordings were obtained at waist level with the assumption that the physician would be positioned on the patient's right side to maneuver the catheters inserted through the femoral or subclavian veins. Exposure rates for the physician are considerably higher during manipulation of a catheter inserted through a subclavian vein because of closer proximity to the primary beam. Table III compares ra-

diation exposure to a physician working at the subclavian position with and without collimation of the primary beam. As shown, radiation exposure to the physician can be markedly reduced by use of a leaded-acrylic shield that is suspended from the ceiling and positioned between the physician and the fluoroscope.

Effective dose equivalent: Table IV lists the computed organ doses for adults during a representative ablation procedure that requires 55 minutes of image-intensifier-assisted fluoroscopy. The computed doses, which include both primary beam and secondary scattered radiation components as applicable, were derived from appropriate tables of organ doses per unit entrance exposure.[11] The average entrance exposure of the right anterior oblique, anteroposterior, and left anterior oblique projections was used to compute these doses. The gonadal dose is primarily attributable to the relatively brief time the gonads are in the primary beam. The exposure rates to the ovaries during fluoroscopy of the chest is 0.2 to 0.3 mrem/min and for the testes it is 0.01 mrem/min. The results listed in Table IV assume that the gonads were exposed directly to the primary beam for 30 seconds during insertion of catheters from

FIGURE 1. Percentages of patients with brief, intermediate and prolonged fluoroscopy exposure.
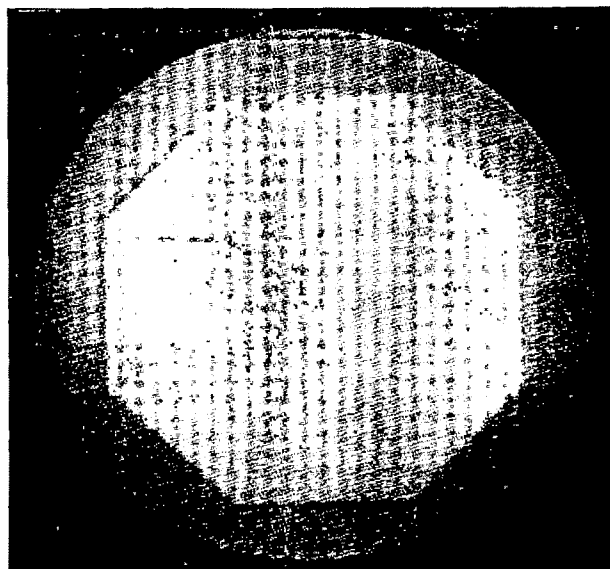
FIGURE 2. Representative fluoroscopic image demonstrating collimation of the primary beam during placement of catheters.

TABLE IV Radiation Dose to Adult Patient	
Organ/Tissue	Dose Equivalent (rems)
Lungs	6.9
Breasts	2.0
Testes	<0.8
Ovaries	0.4
Thyroid	0.4
Bone marrow	1.1
Effective dose equivalent = 1.7 rems.	

TABLE V Comparative Radiation Exposure: Effective Dose Equivalent (rems)	
Arrhythmia ablation procedure	1.7
Recommended annual limit for radiation workers[14]	5.0
Average annual dose in United States[15]	0.3
Medical procedures	
Coronary angiography	1.2
Coronary angioplasty	2.2
Thallium-201 scan[16]	2.1
Technetium-99 radionuclide ventriculogram[16]	0.8

the femoral veins or arteries. For example, the ovarian dose due to scatter from 55 minutes of chest fluoroscopy would be 15 mrem and the dose due to fluoroscopy of the pelvis for 30 seconds would be 375 mrem.

The effective dose equivalent for a representative ablation procedure that required 55 minutes of fluoroscopy is 1.7 rems using the tissue-weighting factors recommended by the International Commission on Radiation Protection.[13] Table V compares the effective dose equivalent of an ablation procedure to recommended dose limits for radiation workers,[14] the annual average dose in the United States due to naturally occurring radiation sources,[15] and the dose associated with other cardiovascular procedures.[16] The effective dose equivalents shown for routine angiography and for angioplasty represent unpublished data from the Mallinckrodt Institute of Radiology and are comparable to results published by other investigators.[17]

Patient risks: The somatic risk of low-level ionizing radiation for acute doses of $\geq$10 rems is cancer induction. The age-averaged, gender-averaged risk of fatal cancer due to x-ray exposure is approximately 1 chance in 126 for an acute dose of 10 rems. If the same risk factor is conservatively assumed for an effective dose equivalent of 1.7 rems, the result is 1 chance in 745 of a fatal cancer due to an electrophysiologic study that required 55 minutes of fluoroscopy. The spontaneous fatal cancer risk in the United States is about 1 chance in 5.[18] Thus, the radiation exposure associated with an ablation procedure may increase the fatal cancer risk on the average by about 1% of the spontaneous risk. The estimated cancer risks from radiation exposure of young adults are greater than for older adults. The age-related risks of cancer induced by radiation for patients with 1 to 4

hours of fluoroscopy are listed in Table VI. In the extreme case, the risk that a fatal cancer will be induced by 4 hours of fluoroscopy in a young female subject (age 1 to 14 years) is as high as 1 chance in 95, which is 4.6% of the expected spontaneous incidence of fatal cancers.

The estimated risk of a serious birth defect in the first generation is estimated to be 30 chances in a million per rem of preconception gonadal radiation (3 × 10^{-5}/rem).[12] The corresponding risk for an arrhythmia ablation procedure is about 12 chances per million or 1 chance in about 80,000, a value that is about 0.1% of the current incidence of serious birth defects in the United States.

Radiation exposure of medical personnel: The calculated effective dose equivalent to the physician who manipulates catheters from the femoral area during an ablation procedure is 1.8 mrems/case (55 minutes of fluoroscopy). This calculation assumes: (1) the field of image is appropriately collimated; (2) the physician maintains a distance of 30 inches from the patient's chest; and (3) standard leaded collars and aprons rated at 0.5 mm lead equivalence are worn. The calculated effective dose equivalent is 2.8 mrems/case if a thyroid collar is not used. A physician who wears a lead apron and collar and performs 250 ablation procedures per year will incur a predicted effective dose equivalent of 450 mrems/year, which is 9% of the recommended annual limit for radiation technologists. The effective dose equivalent is twice as high when the physician is positioned to manipulate a catheter inserted through the subclavian vein, but radiation exposure can be markedly reduced by the use of a leaded-acrylic shield (Table III). The predicted eye exposure is 8 rems unless an

TABLE VI Risk of Fatal Cancer Attributable to Radiation from Fluoroscopy					
Age (yr)	Gender	Fluoroscopy Time			
		1 Hour (%)	2 Hours (%)	3 Hours (%)	4 Hours (%)
1–14	Male	1:460 (1.0)	1:230 (1.9)	1:155 (2.9)	1:115 (3.9)
	Female	1:380 (1.2)	1:190 (2.3)	1:130 (3.5)	1: 95 (4.6)
15–34	Male	1:640 (0.7)	1:320 (1.4)	1:210 (2.1)	1:160 (2.8)
	Female	1:500 (0.9)	1:250 (1.8)	1:165 (2.7)	1:125 (3.6)
35–54	Male	1:980 (0.4)	1:490 (0.9)	1:325 (1.4)	1:250 (1.8)
	Female	1:1087 (0.4)	1:540 (0.8)	1:360 (1.2)	1:270 (1.6)
55–74	Male	1:1220 (0.4)	1:610 (0.7)	1:410 (1.1)	1:305 (1.4)
	Female	1:1520 (0.3)	1:760 (0.6)	1:510 (0.9)	1:380 (1.2)
All	Male	1:760 (0.6)	1:380 (1.2)	1:250 (1.8)	1:190 (2.3)
	Female	1:730 (0.6)	1:360 (1.2)	1:240 (1.8)	1:180 (2.4)

The chance of developing a fatal cancer induced by radiation is listed in the columns. Numbers in parentheses are the percentages of spontaneous fatal malignancies for that age and gender.

effort is made to reduce exposure by means of a leaded acrylic shield or leaded glasses. In this study, the predicted effective dose equivalent for personnel at the monitoring station was 0.6 mrems/case or 162 mrems/250 cases, and for the nurse it was 0.2 mrems/case or 54 mrems/250 cases. Thus, the radiation exposure rates related to ablation procedures for personnel assisting in a busy electrophysiology laboratory are <5% of the recommended annual limit.

DISCUSSION

The risks associated with the radiation exposure required to ablate an arrhythmia have important implications for physicians who recommend this therapy for conditions that are rarely life-threatening. The results of this study demonstrate that the acute radiation dose associated with a typical arrhythmia ablation procedure is comparable to other invasive cardiovascular studies. One difference, however, is that electrophysiologic studies are more likely to be performed in children, adolescents or young adults. This study also establishes that the radiation exposure incurred during an electrophysiologic study carries a very low risk for induction of genetic damage or a fatal malignancy relative to the spontaneous incidence of these disorders. Patients should be informed that they will be exposed to radiation during the procedure, but they can be advised that a typical procedure will not significantly increase their risk for the development of a fatal cancer or a genetic defect in offspring. Obviously, women who are pregnant should not undergo an electrophysiologic study unless their arrhythmias are life-threatening and are refractory to treatment with drugs that can be used safely during pregnancy.

Calkins et al[19] recently reported on the level of radiation exposure to patients and physicians during radiofrequency catheter ablation procedures using thermoluscent sensors placed on the patient and the physician. Despite significant differences in methodology, results of these studies demonstrate similar radiation exposure and projected risk. A major difference in the present study is that direct measurement of the primary beam provides data that can be used to modify technique. The dependency of radiation levels on the fluoroscopic projection used to position catheters, the degree to which the beam is collimated, and appropriate use of shielding have important implications for radiation exposure to patients and medical personnel.

The fluoroscopy time required to perform an ablation procedure was ≤60 minutes in 77% of the patients studied. Protracted use of fluoroscopy (>90 minutes) was required in only 7% of the patients. Although it is likely that fluoroscopy times will become shorter as experience is gained and improved catheter designs facilitate the technique, prolonged radiation exposure will be incurred during the most difficult procedures. The maximal radiation dose to which a patient should be subjected is a matter of judgment that depends on the severity of symptoms, the risks of alternative therapy, and the age of the patient. The estimated cancer risks from radiation exposure of young patients are greater than for older ones. For example, the projected risk per rem

for a woman at age 15 years is >90% of the composite risk, whereas the risk at age 55 years is <40% of the composite risk. For patients who require more than one attempt to ablate the arrhythmia, the radiation exposure associated with the procedures should be considered cumulative. Accordingly, we limit fluoroscopy exposure to 2 hours in young patients with arrhythmias that are not life-threatening. The practice of exposing a young patient with modest symptoms to prolonged fluoroscopy must be questioned. In such cases surgery remains an alternative, or the patient may be advised to wait until the technical limitations of the ablation procedure have been overcome.

It is incumbent on physicians who perform arrhythmia ablation procedures to ensure that the personnel who assist them are not exposed to excessive levels of radiation. In this study the annual radiation dose of physicians who perform 5 ablation procedures each week was projected to be 9% of the recommended annual limit for people whose jobs require radiation exposure. This modest exposure can be markedly reduced by positioning a leaded acrylic shield between the physician and the fluoroscope. The exposure incurred by other personnel in the electrophysiology laboratory is considerably less. These projections assume that the physician uses standard safety precautions and does most of the catheter manipulations from the femoral region. The personnel who assist in the procedure should be stationed as far as practical from the patient and should be appropriately shielded.

The following precautions can substantially limit radiation exposure during arrhythmia ablation procedures: (1) perform fluoroscopy with the beam entering the posterior side of the patient to attenuate radiation to breast and thyroid tissues; (2) reduce the size of the primary radiation field by collimating the field of image; (3) avoid magnification because the entrance dose nearly doubles for 3:2 magnification; (4) select the highest kilovoltage that provides the needed contrast; (5) record catheter positions with video systems instead of cine; (6) maintain the source to entrance distance as long as practical (>20 inches); and (7) conduct periodic inspections and testing of the x-ray unit.

In summary, results of this study demonstrate that patients with Wolff-Parkinson-White syndrome or AV nodal reentry can be treated safely and effectively by using radiofrequency energy to ablate tissue that is critical to the reentrant circuit. Radiation exposure to the patient and to medical personnel is comparable to other cardiovascular procedures and is well within recommended guidelines. Moreover, good technique can substantially reduce radiation exposure. These results support the use of arrhythmia ablation procedures as an alternative to surgery or antiarrhythmic drug therapy in patients with supraventricular arrhythmias that require treatment.

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Baroreceptor-Mediated Release of Vasopressin in Patients with Chronic Congestive Heart Failure and Defective Sympathetic Responsiveness

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In patients with congestive heart failure (CHF), overactivity of the sympathetic nervous system may be accompanied by an impairment of the baroreflex control mechanism. To evaluate the reflex responses of the sympathetic nervous system, the renin-angiotensin system and vasopressin release to baroreceptor unloading, 38 patients with left ventricular dysfunction were studied. Hemodynamic data, and plasma norepinephrine, renin activity and vasopressin concentrations were measured before and 60 minutes after administration of high-dose hydralazine (0.4 mg/kg intravenously). On the basis of blood pressure response to vasodilator administration, patients were divided arbitrarily into those with a decrease in mean arterial blood pressure ≥15 mm Hg (group A; n = 12) and those with a decrease <15 mm Hg (group B; n = 26) compared with control values. In response to hydralazine, heart rate decreased in group A from 100 to 92 beats/min (p <0.001) and increased in group B from 90 to 96 beats/min (p <0.05). In group A, hemodynamic changes induced by hydralazine were accompanied by a decrease in plasma norepinephrine from 822 to 518 pg/ml (p <0.01) and an increase in plasma vasopressin from 8.4 to 45.2 pg/ml (p <0.001). In group B, plasma norepinephrine and vasopressin did not change significantly (407 vs 447, and 8.4 vs 8.3 pg/ml, respectively). Plasma renin activity remained unchanged in group A and increased in group B (p <0.001). The data show that baroreceptor-mediated release of vasopressin is not impaired in patients with CHF and a defective sympathetic reflex control mechanism. Thus, baroreceptor-mediated vasopressin release may represent a protective mechanism to maintain systemic blood pressure in a subgroup of patients with severe CHF.

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The autonomic nervous system has a major role in the maintenance of arterial blood pressure. Furthermore, other neurohormonal systems such as the renin-angiotensin system and nonosmolar release of vasopressin appear to be important backup mechanisms in blood pressure regulation.[1,2] In patients with congestive heart failure (CHF) these vasopressor systems may be activated to maintain circulatory homeostasis.[3,4] When blood pressure is reduced in these patients due to vasodilation, a reflex increase in sympathetic nervous activity is not usually present, indicating an impairment of reflex responsiveness to baroreceptor unloading.[5-8] Prior investigations comparing reflex responses of neurohormonal vasopressor systems with baroreceptor unloading in CHF yielded conflicting results.[7,9-12] Thus, the reflex responses of neurohormonal systems in patients with CHF were studied. A high dose of hydralazine was used to unload arterial baroreceptors, and the drug-induced decrease in arterial blood pressure was related to the reflex responses of plasma norepinephrine, renin activity and vasopressin in patients with severe left ventricular dysfunction. Hydralazine was selected because it acts on arteriolar smooth muscle without directly affecting neurohormonal systems.

METHODS

Patients: This study comprised 38 consecutive patients (36 men and 2 women, age range 26 to 78 years, mean 52) undergoing cardiac catheterization and coronary angiography for evaluation of chest pain or CHF, or both. All patients had class III or IV CHF (New York Heart Association criteria)[13] due to severely impaired left ventricular function (ejection fraction 0.35). The causes of CHF were idiopathic dilated cardiomyopathy (n = 30) or coronary artery disease (n = 8). Left ventricular ejection fraction was calculated using the area-length method.[14] Patients with mitral incompetence exceeding grade 1+ of regurgitation (as determined angiographically)[15] were excluded. Twelve patients with atypical angina, but with normal coronary angiograms and left ventricular function and no detectable congenital or valvular heart disease served as controls.

Procedures and measurements: The protocol was approved by the ethical committee of the University of Heidelberg, and all patients gave informed consent. Measurements before and after hydralazine administration were obtained in the postabsorptive state without premedications between 2 and 4 P.M. at a special re-

TABLE I Hemodynamic Data of Study Patients Before and After Hydralazine Administration					
		All Patients (n = 38)	Group A (n = 12)	Group B (n = 26)	p Value (A vs B)
Mean arterial blood	C	98 ± 12	105 ± 15	95 ± 9*	NS
pressure (mm Hg)	H	86 ± 11*	76 ± 10	90 ± 7*	<0.001
Heart rate	C	93 ± 15	100 ± 13	90 ± 16	NS
(beats/min)	H	95 ± 14	92 ± 12*	96 ± 15†	NS
Cardiac index	C	2.3 ± 0.6	2.0 ± 0.4	2.4 ± 0.6	NS
(L/min/m²)	H	3.7 ± 0.4*	3.3 ± 0.4*	3.9 ± 0.8*	NS
Stroke volume index	C	25 ± 8	21 ± 6	26 ± 8	NS
(ml/m²)	H	39 ± 8*	36 ± 8*	40 ± 8*	NS
Left ventricular filling	C	27 ± 8	30 ± 8	26 ± 7	NS
pressure (mm Hg)	H	23 ± 8‡	19 ± 6*	24 ± 7	NS
Mean right atrial	C	8 ± 4	9 ± 3	8 ± 4	NS
pressure (mm Hg)	H	7 ± 4	6 ± 2*	8 ± 4	NS
Systemic vascular resistance	C	1,911 ± 599	2,220 ± 653	1,768 ± 529	NS
(dynes · s · cm⁻⁵)	H	984 ± 287*	970 ± 238*	991 ± 311*	NS

*p <0.001; †p <0.05; ‡p <0.01 (C vs H).
Values are mean ± SD.
C = control values; H = values after hydralazine; NS = not significant.

search laboratory. Patients continued to receive doses of diuretics and digitalis. Most patients had no maintenance therapy with vasodilators before the study. In 3 patients receiving captopril and in 5 receiving nitrates or dihydralazine, or both, vasodilators were withheld for ≥3 days. No patient had evidence of deterioration during vasodilator withdrawal.

Right-sided heart catheterization was performed in all patients using a triple-lumen Swan-Ganz catheter through which measurements of right atrial, and pulmonary arterial and capillary wedge pressures were obtained. Cardiac output was determined by the thermodilution method. Arterial pressures were monitored by the standard cuff method. Derived hemodynamic variables were calculated as follows: mean arterial pressure = ⅓ (systolic + 2 × diastolic pressure); cardiac index = cardiac output/body surface area; stroke volume index = cardiac index/heart rate; and systemic vascular resistance = 80 × (mean arterial pressure − mean right atrial pressure)/cardiac output.

Blood specimens for plasma hormone analysis were obtained from the pulmonary artery. Samples were collected in heparinized tubes and immediately placed on ice. Plasma was then separated by centrifugation at 4°C within 5 minutes and stored at −80°C for analysis. Plasma norepinephrine was measured radioenzymatically,[16] and plasma renin activity and arginine vasopressin were determined by radioimmunoassays.[17,18] Plasma osmolality was measured using the freezing point method.

Before control hemodynamic data and plasma hormone values were obtained, patients rested in a supine position for 30 minutes. After control measurements were obtained, patients were given 0.4 mg/kg hydralazine intravenously over a period of 15 minutes with constant monitoring of blood pressure and heart rate. Measurements of hemodynamic values and plasma hormones were repeated 45 minutes later.

Statistical methods: All results are expressed as mean ± SD. Intergroup differences were analyzed using Student's t or Wilcoxon's test for unpaired data, or by the chi-square method for categorical data. The signifi-

cance of the responses to hydralazine administration was assessed with Student's t or Wilcoxon's test for paired observations. When multiple comparisons were obtained in the same group of data, the critical value of t was corrected using the Bonferroni method.[19] Relations between different variables were calculated by means of least-square linear regression analysis.

RESULTS

Classification of patients and baseline hemodynamics: Patients were divided arbitrarily on the basis of blood pressure responses to hydralazine administration into those with a decrease in mean arterial blood pressure ≥15 mm Hg (group A) and those with a decrease <15 mm Hg or no decrease (group B) compared with control values. There was no significant difference between group A and B patients regarding age, sex, underlying heart disease or functional class. Left ventricular ejection fraction was lower in group A than in B (0.19 ± 0.06 vs 0.24 ± 0.07; p <0.05). Hemodynamic data before and after hydralazine administration are listed in Table I. Initial mean arterial blood pressure, heart rate, left ventricular filling pressure and systemic vascular resistance tended to be higher, and cardiac and stroke volume indexes tended to be lower in group A than in B, but the differences were not significant.

Hemodynamic responses to hydralazine: By definition, the drug-induced reduction in mean arterial blood pressure was greater in group A than in B (−28 vs −5%). However, a reflex increase in heart rate after hydralazine was observed only in group B. In contrast, group A patients had a significant decrease in heart rate after hydralazine, despite the marked reduction in systemic blood pressure. However, if group A and B patients are considered together, there is no significant change in heart rate after hydralazine administration. Systemic vascular resistance decreased more in group A than in B (−56 vs −44%; p <0.05). The increases in cardiac output and stroke volume after hydralazine were similar in both groups. Left ventricular filling and mean right atrial pressures decreased significantly in group A, but not in B.

TABLE II Plasma Hormones in Study Patients Before and After Hydralazine Administration					
		All Patients (n = 38)	Group A (n = 12)	Group B (n = 26)	p Value (A vs B)
Plasma norepinephrine	C	538 ± 348	822 ± 406	407 ± 226	<0.001
(pg/ml)	H	469 ± 238	518 ± 276*	447 = 220	NS
Plasma renin activity	C	9.6 ± 19.4	20.0 ± 34.2	5.3 ± 5.0	NS
(ng/ml/hr)	H	16.1 ± 21.1†	23.2 ± 33.8	13.1 ± 13.2‡	NS
Plasma vasopressin	C	8.4 ± 6.6	8.4 ± 7.5	8.4 ± 6.2	NS
(pg/ml)	H	20.2 ± 23.3†	45.2 ± 26.3‡	83. ± 6.0	<0.001

*p <0.01; †p <0.05; ‡p <0.001 (C vs H).
Values are mean ± SD.
Abbreviations as in Table I.

Plasma hormones: Values for plasma hormones before and after hydralazine are listed in Table II. Baseline plasma norepinephrine levels in group A were substantially higher than in B. Baseline plasma renin activity also tended to be higher in group A than in B. There was a large amount of heterogeneity in the renin values, ranging from very suppressed to markedly elevated levels. No significant difference was found with respect to plasma vasopressin baseline values between the groups. Baseline values for all plasma hormones tested in groups A and B were significantly higher (p <0.05) than those of control patients (norepinephrine 199 ± 26 pg/ml, plasma renin activity 1.3 ± 0.34 ng/ml/hour, and plasma vasopressin 4.7 ± 0.4 pg/ml). In group A, the hemodynamic changes induced by hydralazine were accompanied by a marked decrease in plasma norepinephrine levels (−37%; p <0.01) and a significant increase in plasma vasopressin (438%; p <0.001), whereas plasma renin activity remained unchanged. In contrast, in group B, plasma norepinephrine tended to increase (10%; p = not significant) and plasma renin activity increased significantly by 147% (p <0.001) after hydralazine, whereas plasma vasopressin did not change. Plasma osmolality was not different between the groups and did not change after vasodilation.

Changes in hemodynamics could be related to changes in plasma hormones. Figure 1 shows the plots between the changes in mean arterial blood pressure and plasma hormone levels in the patients investigated. There was a highly significant correlation between the reduction in mean blood pressure and the increase in plasma vasopressin concentration, and a poor inverse correlation between the decrease in blood pressure and the changes in plasma norepinephrine. No significant correlation was found between the changes in blood pressure and plasma renin activity after hydralazine. Furthermore, there was a weak but significant correlation between changes in vasopressin concentrations and left ventricular filling pressures (r = 0.41; p <0.05). In contrast, there was no significant relation between changes in vasopressin levels and right atrial pressures (r = 0.14; p = not significant).

DISCUSSION

This study presents the first evidence that arterial baroreceptor unloading may induce a dissociation between reflex responses of the sympathetic nervous sys-

tem and vasopressin release in patients with severe CHF.

Overactivity of vasoconstrictor mechanisms: Virtually all patients in the present investigation had elevated baseline plasma norepinephrine concentrations compared with those of control subjects. These findings confirm previous observations suggesting overactivity of the sympathetic nervous system in CHF and a direct correlation between plasma norepinephrine and the degree of hemodynamic deterioration.[20,21] Similarly, plasma renin activity and vasopressin concentrations were increased in a large proportion of patients studied, but no significant differences were noted between groups A and B regarding these hormones. Therefore, our data are consistent with those of previous studies describing elevated plasma levels of renin and vasopressin without correlation with hemodynamic variables in patients with CHF.[21,22]

Reflex responses of efferent sympathetic activity: Although the mechanism that causes activation of the sympathetic nervous system in CHF is not fully understood, excitatory sympathetic reflexes initiated by peripheral hypoperfusion appear to have a major role.[23] Therefore, improved tissue perfusion due to vasodilator therapy can be expected to reduce sympathetic outflow. However, unloading of arterial baroreceptors may result in reflex activation of the sympathetic nervous system. Therefore, the response of the sympathetic nervous system to hydralazine-induced vasodilation in patients with CHF is the result of the following 2 opposing mechanisms: (1) reduction of excitatory influences of sympathetic outflow due to hemodynamic improvement, and (2) reflex stimulation of efferent sympathetic activity mediated by arterial baroreceptors.

This concept is supported by the data of the present study. In group A patients (those with the most severe degree of CHF), plasma norepinephrine decreased consistently, whereas norepinephrine levels tended to increase in the remaining patients. In group A, a marked defect in baroreceptor control mechanisms could be expected.[24] It may be postulated that the excitatory influence of unloading of arterial baroreceptors on sympathetic outflow is overridden by the inhibition of efferent sympathetic activity resulting from hemodynamic improvement in group A patients. These findings corroborate numerous investigations suggesting impaired baroreceptor control of systemic circulation in CHF.[5–7,25]

The substantial decrease in mean arterial blood pressure observed in group A may be due to this abnormal neurohormonal response.

In contrast, most group B patients had an essentially normal increase in heart rate and a trend toward increased norepinephrine levels in response to hydralazine. In these patients, the baroreceptor reflex can be assumed to be less impaired than in group A patients. This reflex activation of the sympathetic nervous system due to vasodilator therapy in group B patients is consistent with the findings of Packer et al[8] who observed rebound hemodynamic events after withdrawal of nitroprusside in patients with severe CHF.

Plasma vasopressin response to arterial baroreceptor unloading: In healthy humans, a reduction in mean arterial blood pressure of 10 to 15% produces little or no increase in plasma vasopressin levels, whereas a more marked hypotension increases vasopressin in an exponential fashion.[26] A similar relation between decrease in mean arterial blood pressure and increase in vasopressin levels is shown in this study. Therefore, the results indicate that the release of vasopressin in response to a significant decrease in blood pressure appears not to be impaired in patients with CHF.

Our data confirm and extend some observations of Uretsky et al[27] and Borghi et al.[28] These investigators reported only a weak correlation between changes in mean arterial pressure and plasma vasopressin after a drug-induced vasodilation. In a similar study, Francis et al[9] could not find any significant changes in vasopressin levels after nitoprusside and captopril administration in patients with CHF. In their study, the drug-induced reduction in mean arterial blood pressure was not >12 mm Hg. The results of these studies are in agreement with our findings. The drug-induced decrease in blood pressure was too small to induce major changes in vasopressin release in these previous studies.

The increase of plasma vasopressin in group A after vasodilation appears to be largely mediated by afferents originating from arterial baroreceptors. This assumption is supported by the close relation between decrease in mean arterial pressure and increase in vasopressin. Unloading of cardiopulmonary receptors may have an additional role in vasopressin release after hydralazine. However, the correlation between the changes in left ventricular filling pressures and plasma vasopressin levels is rather weak. Plasma renin activity in group A patients did not change significantly after hydralazine administration. The increase in plasma vasopressin in these patients is evidently not mediated by the renin-angiotensin system.

Possible role of vasopressin in blood pressure regulation: The autonomic nervous system has a significant role in the regulation of arterial blood pressure. Alterations in blood pressure control are known to occur in patients with CHF.[3,5-7] During tilting, some patients with CHF have a major reduction in arterial pressure similar to that in idiopathic orthostatic hypotension.[25] In group A, the reflex response of heart rate was blunted, and plasma norepinephrine concentrations did not increase in response to a marked unloading of arterial

baroreceptors, whereas vasopressin release was not impaired in comparison with that in healthy subjects. Because vasopressin can exert direct vasoconstrictor actions at plasma concentrations observed after hydrala-
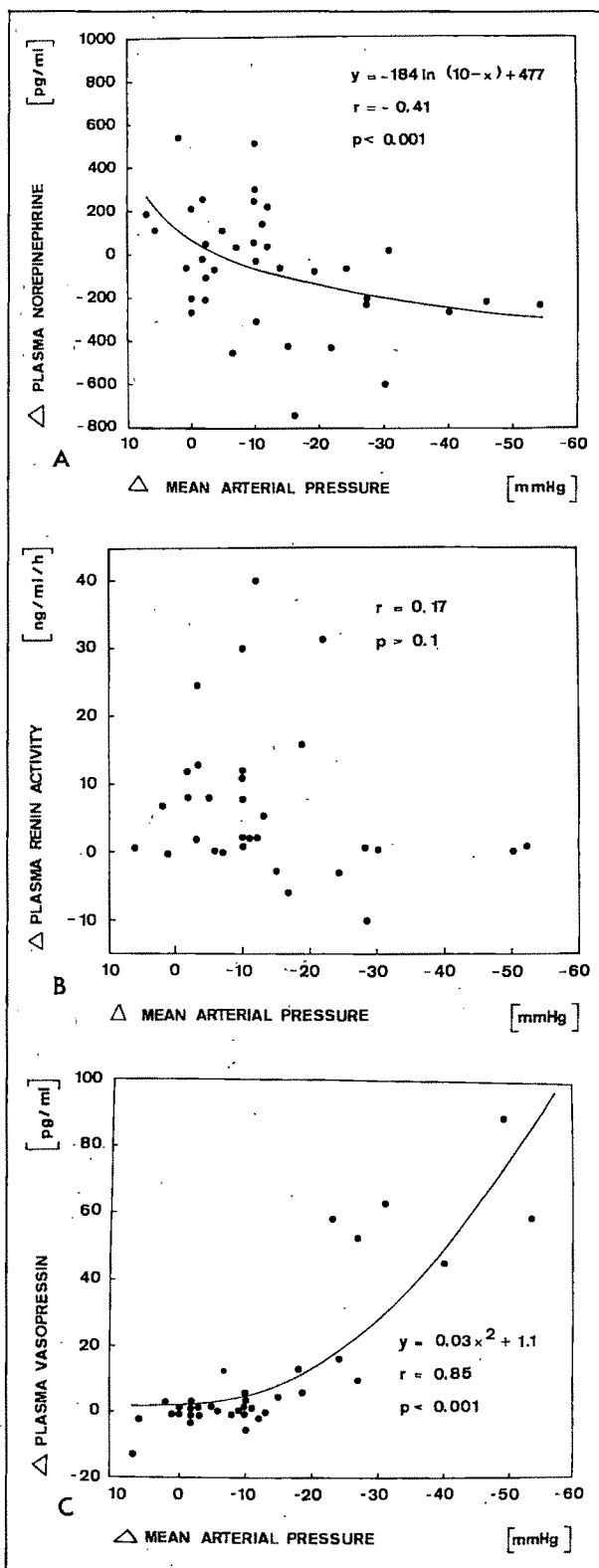

FIGURE 1. Correlations between changes (Δ) in mean arterial blood pressure and plasma hormone concentrations after hydralazine administration.

zine in group A,[29] endogenous vasopressin may have an important role in maintaining systemic pressure in this subgroup of patients with CHF. This view is supported by Möhring et al[30] who observed greatly enhanced pressure responses to vasopressin in patients with idiopathic orthostatic hypotension.

Implications: The results of this study suggest that the baroreceptor-mediated release of vasopressin is unimpaired in patients with CHF and defective sympathetic nervous reflex control mechanisms. Therefore, baroreceptor unloading may induce a substantial increase in plasma vasopressin without a reflex increase in sympathetic activity in these patients. Thus, the vasopressin system may have a protective role in the maintenance of arterial blood pressure in severe CHF.

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Rate of Progression of Valvular Aortic Stenosis in Adults

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Until recently the hemodynamic severity of valvular aortic stenosis (AS) was evaluated only by cardiac catheterization. Now, Doppler echocardiography allows a noninvasive and accurate assessment of AS severity and can be used to study its progression with time. The progression of AS was assessed during a follow-up period of 6 to 45 months (mean 18) by serial Doppler examinations in 45 adult patients (21 men and 24 women, mean age 72 ± 10 years) with isolated AS. The following parameters were serially measured: left ventricular outflow tract diameter and velocity by pulsed Doppler, peak velocity of aortic flow by continuous-wave Doppler, to calculate peak gradient by the modified Bernoulli equation, and aortic valvular area by the continuity equation. At the initial observation, 13 of 45 patients (29%) were symptomatic (1 angina, 1 syncope and 11 dyspnea); during follow-up, 25 (55%) developed new symptoms or worsening of the previous ones (5 angina, 3 syncope and 17 dyspnea); 11 underwent aortic valve replacement and 3 died from cardiac events. Baseline peak velocity and gradient ranged between 2.5 and 6.6 m/s, and 25 and 174 mm Hg, respectively; aortic area ranged between 0.35 and 1.6 cm². With time, mean peak velocity and gradient increased significantly from 4 ± 0.7 to 4.7 ± 0.8 m/s (p <0.01), and 64 ± 30 to 88 ± 30 mm Hg (p <0.01), respectively. A concomitant reduction in mean aortic area occurred (0.75 ± 0.3 to 0.6 ± 0.15 cm²; p <0.01). The rate of progression of AS (−0.72 to +0.14 cm²/year, mean −0.1 ± 0.13) was variable among patients and did not relate to age, sex, follow-up duration or symptoms. Patients with a reduction in left ventricular systolic function had a faster progression than did those with normal systolic function. In conclusion, a significant progression of AS may occur and a mild or moderate stenosis can become critical after a few years. Doppler echocardiography appears to be the ideal method for follow-up and can add new insights to the natural history of the disease.

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Until recently cardiac catheterization was the "reference" method to assess the severity of valvular aortic stenosis (AS) and its changes with time[1-8]; being invasive, however, this method could not be repeated indefinitely to evaluate the hemodynamic progression of the disease. Previous studies were performed in small groups of patients with AS in whom cardiac catheterization was repeated (once and rarely twice) usually because of a change in clinical status such as the appearance of symptoms.[3-7] This bias has limited our understanding of the natural history of AS, mainly in asymptomatic subjects. Currently, Doppler echocardiography allows an accurate assessment of the severity of AS by calculation of the transvalvular pressure gradient and aortic area[9-13]; therefore, this noninvasive technique can be repeated easily to examine the progression of disease with time.[14,15] This study analyzes the rate of progression of AS, using Doppler echocardiographic criteria.

METHODS

Study group: We prospectively followed up 45 adult subjects (24 women and 21 men, mean age 72 ± 10 years, range 42 to 90) with AS. All subjects gave informed consent. Criteria for diagnosis of AS included both physical signs, such as a decreased intensity of the second sound and a harsh systolic ejection murmur, and the presence on Doppler echocardiographic examination of thickened aortic cusps with reduced mobility and a maximal aortic jet velocity ≥2.5 m/s. On the basis of clinical history and 2-dimensional echocardiographic findings, the origin of AS was considered rheumatic in 7 patients and degenerative-calcific in 34; in 4 of the latter group, a bicuspid aortic valve was evident. Finally, the remaining 4 patients had a markedly calcific aortic valve and root, so no cause of AS was clearly identifiable.

Doppler echocardiographic examination: Each patient underwent a complete echo-Doppler examination at entry in the study and serially during a follow-up period of 6 to 45 months (mean 18); the ultrasound evaluation was always performed on request of the cardiologist or internist responsible for the care of the patient. These physicians also provided us with information on the clinical status of patients (appearance or worsening of symptoms, cause of death, and valve replacement) during follow-up. At least 3 echocardiograms were obtained in all but 5 patients in whom only 2 sets of data were available. Two commercial instruments (UM-8 and UM-9, Advanced Technology Laboratories) were used, and the following parameters were measured to assess the severity of AS: (1) peak velocity

of aortic jet, recorded with a nonimaging continuous-wave Doppler transducer from the ultrasound windows (apical, subcostal, right parasternal and suprasternal) that provided the highest velocity signal and the best envelope curve. Because the optimal signal was assumed to be near parallel to the direction of maximal transvalvular flow velocity, no angle correction was performed. From peak velocity (m/s), peak aortic pressure gradient (mm Hg) was calculated according to the modified Bernoulli equation.[9] (2) Aortic valve area was derived by the continuity equation, taking into account, besides the peak velocity of aortic jet, the diameter of the left ventricular (LV) outflow tract (measured from the 2-dimensional parasternal long-axis plane) and the flow velocity in the LV outflow tract (recorded with pulsed Doppler from an apical approach).[10–13] Furthermore, LV end-diastolic and end-systolic diameters and frac-

tional shortening on the transverse plane were measured according to the recommendations of the American Society of Echocardiography[16] for the evaluation of LV function.

All echocardiograms were obtained by the same physician (PF); intraobserver variability was assessed in an independent group of 10 adults with AS. Two Doppler echocardiographic examinations were obtained in each patient, with an interval of 7 to 15 days without changes in clinical status. Mean coefficients of variation were 3% for peak velocity, 1.5% for LV outflow tract diameter, and 5% for aortic area.

Statistical analysis: Data are expressed as mean ± SD. Rates of change of Doppler parameters of AS severity were corrected for the duration of follow-up and indexed for the year of follow-up. Assessment of changes over time was obtained using paired t test to

TABLE I Clinical and Doppler Echocardiographic Data in 45 Patients with Aortic Stenosis

Pt.	Age (yr) & Sex	Etiology	Follow-Up (mos)	Maximal Velocity (m/s) Entry	Maximal Velocity (m/s) Last	Aortic Valve Area (cm²) Entry	Aortic Valve Area (cm²) Last	LV Fractional Shortening (%) (last)
1	42M	Rheumatic	24	3	3.9	1.2	0.9	50
2	54M	Rheumatic	9	4.5	4.4	0.9	0.6	20
3	55M	Bicuspid	17	4.5	5	0.75	0.65	52
4	55M	Bicuspid	25	3.2	4	1.4	1.1	50
5	59F	Rheumatic	11	4.3	4.8	0.7	0.6	50
6	61F	Rheumatic	33	6.6	6.8	0.4	0.4	44
7	61F	Rheumatic	18	4.1	5.5	0.7	0.5	50
8	62M		34	3.5	4.3	0.9	0.75	45
9	64F	Rheumatic	11	4.3	4.7	0.65	0.6	35
10	65M		24	3	4.3	1.1	0.8	46
11	65F		14	4.3	5	0.45	0.4	50
12	67M		10	3.6	4.5	0.7	0.55	38
13	69F	Rheumatic	24	4.4	5.4	0.6	0.5	50
14	69M	Degenerative	34	3.3	4.3	0.85	0.65	46
15	70F	Degenerative	19	3.5	3.3	0.75	0.8	43
16	70M	Degenerative	25	3	3.9	0.9	0.7	32
17	71M	Bicuspid	7	4.3	4.7	0.75	0.65	23
18	71M	Degenerative	19	4.6	5	0.6	0.55	32
19	72F	Degenerative	12	5.1	5.6	0.4	0.35	48
20	72M	Degenerative	33	3.5	4.9	1.6	0.8	33
21	72F	Degenerative	7	4.7	5.2	0.85	0.75	21
22	73F	Degenerative	13	3.4	4.1	0.65	0.55	40
23	73F	Bicuspid	6	5.2	5.1	0.4	0.4	21
24	73F	Degenerative	6	4	4	0.4	0.4	45
25	74F	Degenerative	21	2.7	4	0.95	0.65	50
26	74F	Degenerative	18	3.2	3.6	0.95	0.85	50
27	75F	Degenerative	13	5	5.4	0.5	0.45	54
28	76M	Degenerative	45	3.5	4.5	0.95	0.75	50
29	77M	Degenerative	31	2.5	3.8	1.3	0.65	22
30	77F	Degenerative	16	4.7	5.5	0.6	0.5	42
31	77M	Degenerative	16	5.5	5.8	0.4	0.4	50
32	77M	Degenerative	12	5	5	0.7	0.7	31
33	79F	Degenerative	31	2.7	4.9	1	0.6	45
34	79F	Degenerative	16	5.7	6.3	0.75	0.65	42
35	79F	Degenerative	30	4	5.3	0.6	0.45	38
36	79F	Degenerative	21	3.5	5.3	0.45	0.45	22
37	80M	Degenerative	11	3.2	3.5	0.6	0.7	25
38	81M	Degenerative	22	4	4.9	1	0.7	41
39	81F	Degenerative	12	4.8	5.3	0.55	0.45	52
40	82F	Degenerative	12	3.2	3.4	0.85	0.8	43
41	82F	Degenerative	9	4.5	4.7	0.35	0.3	23
42	85F	Degenerative	7	3.7	3.9	0.8	0.75	41
43	87M	Degenerative	10	4.7	4.6	0.65	0.5	23
44	87F	Degenerative	18	4.6	5	0.4	0.3	36
45	90M	Degenerative	9	3.1	3.5	0.95	0.4	16

LV = left ventricular.
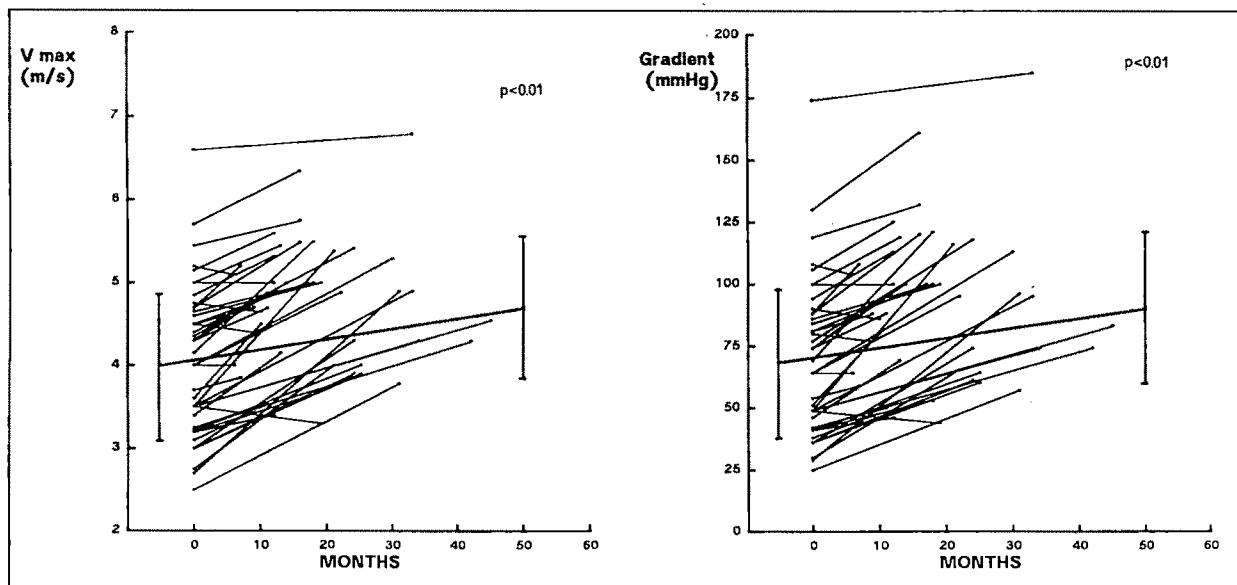
FIGURE 1. Change in maximal aortic jet velocity (V max) and pressure gradient during follow-up in 45 patients. See text for details.

compare the results of the initial and last echocardiographic examinations. Comparison of means between subgroups (with and without symptoms, with and without LV systolic dysfunction, and so forth) was performed with an unpaired *t* test. The effects of clinical features on the progression of AS were evaluated by linear regression analysis.

RESULTS

Clinical data: At entry to the study, 13 of 50 patients (29%) had symptoms probably due to AS (1 angina, 1 syncope and 11 dyspnea). During follow-up, 25 patients (55%) developed new symptoms or worsening of preexisting ones. The most frequent symptoms were angina (n = 5), syncope (n = 3) and dyspnea (n = 17); 13 patients underwent aortic valve replacement and 3 died (1 died suddenly after the recent onset of angina, and 2 died from progressive and refractory congestive heart failure).

Doppler echocardiographic data (Table I): At the initial study, mean peak velocity was 4.0 ± 0.7 m/s (range 2.5 to 6.6) corresponding with a peak pressure gradient of 64 ± 30 mm Hg (range 25 to 174); the aortic area ranged between 0.35 and 1.6 cm² (mean 0.75 ± 0.3). A trivial or mild aortic regurgitation was recorded by pulsed Doppler in 29 patients (64%). The last echocardiographic examination showed a peak velocity and pressure gradient significantly increased to 4.7 ± 0.8 m/s (range 3.3 to 6.8; p <0.01) and 88 ± 30 mm Hg (range 44 to 185; p <0.01), respectively (Figure 1). Furthermore, aortic area was significantly reduced during follow-up to 0.6 ± 0.15 cm² (range 0.3 to 1.1; p <0.01) (Figure 2). No changes in the prevalence and severity of aortic regurgitation were observed with sequential echocardiograms.

An increase in peak velocity and pressure gradient was seen in most patients (39 of 45; 86.6%), whereas 6 had either no change or a decrease during follow-up; however, the valve area in the latter patients mildly in-

creased in 2 (within the intraobserver mean coefficient of variation), remained unchanged in 2 and decreased in the remaining 2 owing to a concomitant reduction of LV outflow tract velocity.

The rate of progression of AS severity was expressed by the changes in Doppler parameters indexed for the year of follow-up; peak velocity increased with time at a mean rate of 0.4 ± 0.3 m/s/year (range −2 to 1) and peak gradient increased at a mean of 15 ± 10 mm Hg/year (range −8 to 38). However, aortic area decreased at a rate of −0.1 ± 0.13 cm²/year (range −0.72 to 0.14). The rate of change of AS severity was lower than the mean coefficient of variation (5% for valve area; see Methods) in 8 patients; however, no significant differences in the rate of progression were observed between the study group considered as a whole

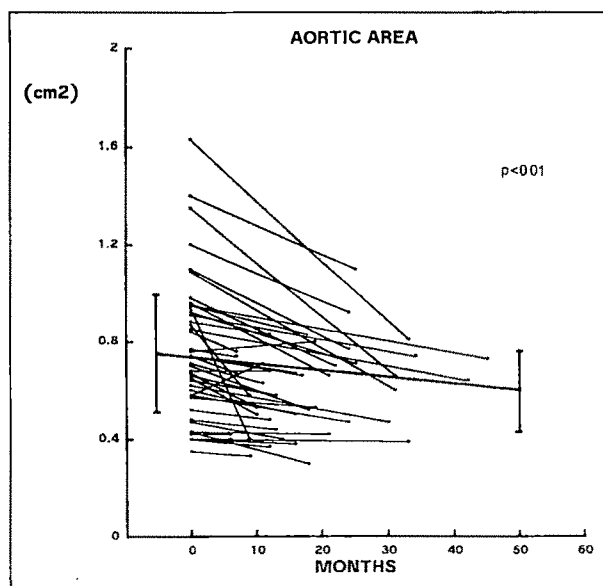**FIGURE 2. Change in aortic valve area during follow-up in 45 patients. See text for details.**
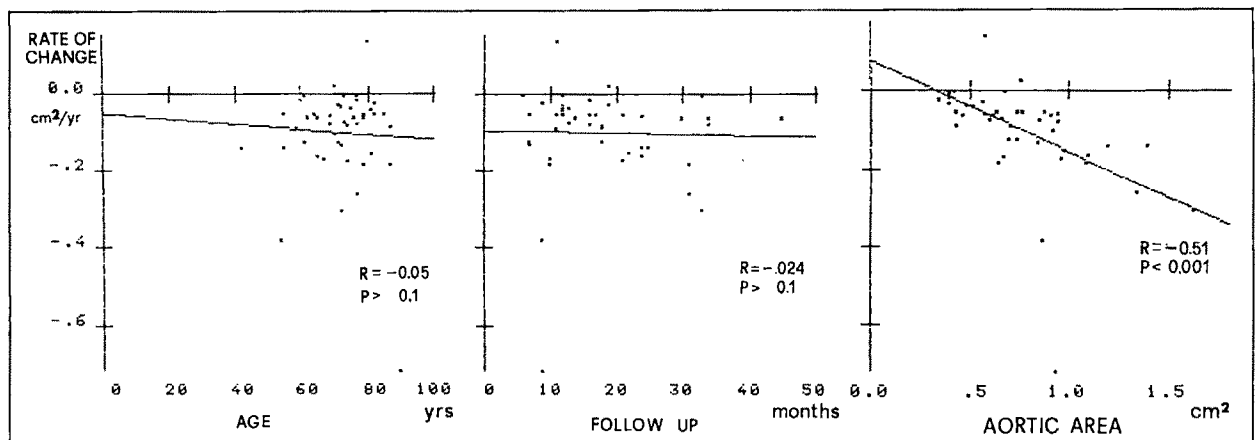
FIGURE 3. Linear regression analysis between rate of progression of aortic stenosis (expressed as rate of change of valve area/year of follow-up [y axis]) and age of patients (left), duration of follow-up (middle), and aortic area at entry (right) (x axis). Rate of progression showed only an inverse relation of low degree (r = −0.51) with severity of aortic stenosis at initial Doppler echocardiographic examination.

TABLE II Clinical and Doppler Echocardiographic Features According to Left Ventricular Systolic Function

	Normal (n = 35)	Reduced (n = 10)	p Value
Age (yr)	71 ± 10	76 ± 10	NS
Women/men	20/15	4/6	NS
LV end-diastolic diameter (mm)	45 ± 6.5	61 ± 7	0.001
LV fractional shortening (%)	44 ± 6.5	21 ± 3.5	0.001
Aortic area (cm²)			
Entry	0.75 ± 0.3	0.7 ± 0.3	NS
Last	0.6 ± 0.1	0.55 ± 0.15	NS
Follow-up (mos)	20 ± 9	12 ± 8	0.05
Rate of change in area (cm²/yr)	−0.08 ± 0.065	−0.17 ± 0.24	0.05

Values are expressed as group means ± 1 SD. See text for details.
LV = left ventricular; NS = not significant.

and when these 8 patients were excluded. Therefore, in the subsequent analysis of results, the data presented refer to the entire study group. The rate of progression of AS was variable among patients and not related to sex, age or duration of follow-up (Figure 3). An inverse relation of low degree (r = −0.51), but statistically significant, was found between the rate of change of AS severity and the initial value of aortic area (Figure 3). The appearance or worsening of symptoms did not enable the identification of patients with more rapid progression of AS. In fact, although symptomatic patients had a smaller aortic area than did asymptomatic ones at the last echocardiographic examination (0.55 ± 0.15 vs 0.65 ± 0.15 cm²), the rate of change of aortic area in the former group was −0.11 ± 0.16 cm²/year and in the latter −0.09 ± 0.06 cm²/year (p = not significant). On the other hand, the subgroup of 10 patients with a reduction of LV systolic function (identified by LV fractional shortening ≤25%) had a rate of change of aortic area significantly greater (−0.17 ± 0.24 cm²/year) than that of those with preserved LV systolic function (−0.08 ± 0.065 cm²/year; p <0.05) (Table II).

DISCUSSION

The results obtained in this prospective study of 45 patients with AS examined by Doppler echocardiography for a mean period of 18 months show that the severity of AS increases with time at a mean rate of 0.1 cm²/year, but the rate of progression is variable among patients, so that mild or moderate AS can become critical in a few years. Similar results were found by previous studies using cardiac catheterization.[3–7] In accordance with these other studies,[6,7] we found no significant relation between the rate of progression and clinical features such as age, sex and duration of follow-up. Furthermore, as in other studies, the rate of change of AS severity was not different between symptomatic and asymptomatic patients.[4–6] Different results were reported in 2 recent studies that also used Doppler echocardiography. Otto et al[14] found that the appearance of clinical symptoms identified patients with a higher rate of progression (expressed by the rate of increase of pressure gradient or the rate of reduction of valve area, or both). Furthermore, Roger et al[15] found that the worsening of symptoms was related to the increase of pressure gradient.

In our study a significantly higher rate of progression of AS was observed in patients with a reduction of LV systolic function compared to those with normal systolic function. Wagner and Selzer[5] found similar results in their study performed with cardiac catheterization. They hypothesized that a reduction in LV performance (causing a decrease in cardiac output) will reduce the aortic valve opening force; this is another factor responsible for the severity of AS, in addition to the reduction of leaflet mobility. When aortic orifice area is reduced, an impairment of LV systolic function (either due to "afterload mismatch" or secondary to other mechanisms, such as coronary artery disease), by decreasing cardiac output, further reduces valve

area.[5,17] This mechanism of increase of AS severity was found mainly in older patients with degenerative-calcific AS in whom the primary pathologic process affecting the aortic valve is the calcification of the base of the leaflets (without commissural fusion), which become very sensitive to the opening force of LV contraction. We could not statistically evaluate this behavior in our study group because of the small number of patients with rheumatic or congenital AS compared with the degenerative-calcific group. However, the most rapid progression of AS severity (rate of change of aortic area -0.72 cm^2/year) observed in our study was in a 90-year-old man with calcific AS in whom a severe reduction of LV systolic function appeared during follow-up (LV fractional shortening decreased from 36 to 16%).

The role of reduction of cardiac output in determining the severity of AS emphasizes the importance of measuring the valve area, not just the pressure gradient, as an index of AS severity,[18] mainly in follow-up studies. Because valve area depends on pressure gradient as well as transvalvular volume flow (i.e., cardiac output), an increase in the severity of AS may occur, despite no change or even a decrease in pressure gradient, due to a reduction in cardiac output. In 2 of our patients, valve area decreased, despite a reduction in pressure gradient, due to a concomitant reduction of LV outflow tract velocity (see Results); the progression of AS would have been missed if only pressure difference was considered.

Study limitations: The majority of our patients (58%) had an aortic area ≤ 0.75 cm^2 at entry; therefore, the conclusions drawn from this study mainly apply to patients with severe AS. Although we found a significant inverse relation between the initial aortic area and its rate of change during follow-up, according to previous studies,[4,8,17] we recognize that the limited number of patients in our study with aortic area >0.75 cm^2 and the mean duration of follow-up does not allow us to conclude that there is a more rapid progression in patients with mild to moderate AS.

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Comparison of Cardiac Findings in Patients with Mitral Valve Prolapse Who Die Suddenly to Those Who Have Congestive Heart Failure from Mitral Regurgitation and to Those with Fatal Noncardiac Conditions

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Sudden death occurs in a small but important subset of patients with mitral valve prolapse (MVP). Clinical criteria for identifying patients at risk for sudden death have been elusive. To determine if certain morphologic characteristics were present in hearts from patients with sudden cardiac death and MVP, autopsy hearts from persons with sudden death and isolated MVP who were previously asymptomatic or had a history of cardiac arrhythmias (n = 27) were compared with (1) hearts from patients with congestive heart failure (CHF) and mitral regurgitation (MR) secondary to MVP (n = 14), and (2) hearts from persons dying from noncardiac causes in which MVP was an incidental finding (n = 19). Patients who died suddenly were younger than both patients with MR/CHF and incidental cases (37 ± 10 vs 65 ± 16 and 58 ± 21 years, respectively, p <0.001). Mitral valve annular circumference, anterior and posterior mitral valve leaflet lengths, posterior mitral valve thickness, and presence and extent of endocardial plaque were greater in hearts from patients with sudden death than hearts from those with incidental MVP. Hearts from patients with MR/CHF weighed significantly more, had greater left and right atrial cavity sizes and left ventricular cavity diameter than hearts from both sudden death and incidental cases.

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or the Department of Defense.

M itral valve prolapse (MVP) is present in approximately 4% of the general population and is most prevalent in young women.[1-4] Most patients with MVP are asymptomatic or have mild symptoms and signs including occasional palpitations, atypical chest pain, or ventricular or supraventricular ectopy, or a combination of these. In contrast, a subset of patients with MVP develop severe complications resulting from congestive heart failure (CHF) secondary to progressive mitral regurgitation (MR).[5-7] An even smaller group experiences sudden death, with MVP being the only significant pathologic finding at autopsy.[8-13]

In the absence of hemodynamically significant MR, sudden death is an uncommon complication of MVP, occurring at an annual rate of approximately 1.9 to 40/10,000 patients with MVP.[14,15] Although there have been several reports on the pathology of MVP associated with sudden death,[8-13,16] few large studies are available that use control groups and attempt to correlate pathologic cardiac findings with clinical symptoms and outcome.

METHODS

All cases of MVP from 1970 through 1990 accessed to the Department of Cardiovascular Pathology at the Armed Forces Institute of Pathology were reviewed. Charts were evaluated for age, sex, race, symptoms and clinical history. Formalin-fixed gross autopsy hearts were retrieved and examined in a blinded fashion without knowledge of the clinical circumstances of the cause of death. From the clinical history, cases were categorized as follows: (1) persons who died suddenly in whom MVP was the only anatomic abnormality present, with no other cardiac or noncardiac condition present at autopsy that could explain the sudden death; (2) patients with symptoms of CHF and a history of significant MR secondary to MVP; or (3) persons dying of noncardiac causes in whom MVP was an incidental finding at autopsy. Sudden death was defined as unexpected death within 6 hours of a previously witnessed usual state of health. Sudden death patients who had evidence of another potentially fatal cardiac condition, e.g., severe atherosclerosis of the coronary arteries (≥75% luminal cross-sectional narrowing), coronary artery anomalies, myocarditis or right ventricular dysplasia were excluded from analysis.

MVP was defined as increased leaflet length and redundancy with interchordal hooding and leaflet billowing toward the left atrium. In most cases, redundancy of chordae tendineae was present. Evaluation of the mitral valve apparatus consisted of measurements of the mitral valve annulus circumference, the anterior and posterior leaflet lengths, the anterior leaflet thickness, the percentage of the anterior leaflet that demonstrated MVP, the involvement and thickness of each of the 3 scallops of the posterior leaflet, and the presence or absence of endocardial plaques (friction lesions) behind the posterior leaflets. Leaflet length represented the greatest distance from the annular insertion of the valve to the free edge. The thickness of each leaflet was graded on a scale of 0 to 3+, with 0 signifying normal leaflet thickness, and 1 to 3+ representing mild (twice normal leaflet thickness), moderate (three times normal) and severe thickening (severe scarring), respectively. Endocardial plaque (friction lesions) on the posterolateral wall of the left ventricle was graded from 0 to 3+, with 0 signifying no plaque present, and 1 to 3+ corresponding to the presence of plaque behind 1, 2, or all 3 scallops of the posterior mitral valve leaflet, respectively. Histologic sections (n = 18) of the most involved segments of the mitral valves were prepared and examined semiquantitatively for the severity of expanded spongiosa, breaks in the fibrosa, valvular fibrosis and elastic fiber duplication.

The following cardiac characteristics were recorded: heart weight, left and right ventricular wall thicknesses, left ventricular cavity diameter, left and right atrial sizes, and annular circumference of the tricuspid valve. Ventricular wall thickness was measured at the midpapillary muscle level. Atrial size was graded on a 0 to 3+ scale, with 0 signifying normal atrial size, and 1+, 2+ and 3+ corresponding approximately 2, 3 and 4 times normal atrial size.

Statistical analysis: All data are expressed as mean ± standard deviation. Variables among the 3 groups of MVP cases (sudden death, MR/CHF and incidental) were assessed using Tukey's pairwise simultaneous comparison. A p value ≤0.05 was considered significant.

RESULTS

A total of 69 cases were retrieved. Nine cases were excluded for the following reasons: previous extensive dissection and sectioning (n = 5), ≥75% atherosclerotic narrowing of at least 1 coronary artery in persons who died suddenly (n = 3), and simultaneous right ventricular dysplasia with MVP in a patient who died suddenly (n = 1). Thus, 60 cases were available for analysis. There were 27 sudden death cases (13 men, 14 women), 14 MR/CHF cases (10 men, 4 women) and 19 incidental cases (11 men, 8 women). Sudden death patients were significantly younger than both MR/CHF and incidental patients (37 ± 10 vs 65 ± 16 and 58 ± 21 years, respectively; p <0.001). Sex distribution differences among the 3 groups did not reach statistical significance. All but 3 of the hearts were from white persons (3 blacks [1 sudden death, 2 incidental]).

Of the sudden death patients, 5 had a history of MVP on the basis of a systolic click or echocardiogram,

TABLE I Nonmitral Valvular Cardiac Characteristics in Hearts with Mitral Valve Prolapse

	Sudden Death (n = 27)	MR/CHF (n = 14)	Incidental (n = 19)
Heart weight (g)	398 ± 110*	635 ± 140§	373 ± 84
LV wall (cm)	1.5 ± 0.2	1.6 ± 0.4‡	1.3 ± 0.2
RV wall (cm)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.2
LV cavity (cm)	2.4 ± 0.7*	3.7 ± 0.9§	2.3 ± 0.6
RA size (0–3+)	0.9 ± 0.7*	2.1 ± 0.7§	0.9 ± 1.0
LA size (0–3+)	1.4 ± 0.9*	2.9 ± 0.4§	1.4 ± 1.0
TV annulus (cm)	12.3 ± 1.2†	13.0 ± 1.2‡	11.2 ± 2.0

*p ≤0.001 (sudden death vs MR/CHF).
†p ≤0.05 (sudden death vs incidental).
‡p ≤0.05; §p ≤0.001 (MR/CHF vs incidental).
LA = left atrium; LV cavity = left ventricular cavity size; LV wall = left ventricular wall thickness; MR/CHF = mitral regurgitation/congestive heart failure; RA = right atrium; RV wall = right ventricular wall thickness; TV annulus = tricuspid valve annulus circumference.

TABLE II Mitral Valve Characteristics in Hearts with Mitral Valve Prolapse

	Sudden Death (n = 27)	MR/CHF (n = 14)	Incidental (n = 19)
MV annulus (cm)	12.3 ± 1.9†	13.3 ± 1.6§	9.9 ± 1.6
AL length (cm)	2.6 ± 0.4*	2.9 ± 0.6§	2.2 ± 0.4
% AL prolapse	39 ± 32	46 ± 31	22 ± 24
AL thick (0–3+)	1.3 ± 0.9	1.6 ± 0.8	1.2 ± 0.7
PL length (cm)	2.3 ± 0.4*	2.4 ± 0.4‡	1.8 ± 0.6
PL thick (0–3+)			
Posterior scal.	1.0 ± 1.1	1.3 ± 1.2	0.8 ± 0.8
Intermed. scal.	1.8 ± 0.7*	1.8 ± 1.0	1.2 ± 0.7
Anterior scal.	1.2 ± 0.8	1.4 ± 1.3	0.9 ± 0.9
Endocardial plaque severity (0–3+)	1.5 ± 1.0*	1.4 ± 1.0	0.7 ± 0.9

*p ≤0.05; †p ≤0.001 (sudden death vs incidental).
‡p ≤0.05; §p ≤0.001 (MR/CHF vs incidental).
AL thick = anterior leaflet thickness; % AL prolapse = percentage of anterior leaflet prolapsing; Intermed. = intermediate; MV annulus = mitral valve annulus circumference; PL thick = posterior leaflet thickness; scal. = scallop.

or both; 2 had palpitations and 4 had ventricular ectopic activity (with 1 person having a documented history of ventricular tachycardia). The circumstances of death in sudden death patients were as follows: sudden death with exercise (n = 3); sudden death while walking (n = 2); witnessed sudden collapse, no exercise (n = 10); unwitnessed, found dead (n = 12). Of those with witnessed sudden death (15 cases), all were reported to have sudden collapse and did not regain consciousness. No person who died suddenly had a history of congenital prolonged QT syndrome; one sudden death patient had been taking procainamide (for ventricular arrhythmias) for ≥8 years at the time of death. Toxicology screens were negative for drug overdoses. Additionally, 7 patients with MR/CHF experienced ventricular arrhythmias, and 5 had supraventricular arrhythmias.

Of the 19 persons in the incidental group, death occurred as a result of a motor vehicle accident in 7 cases; from police reports, the causes of the accidents were determined to have been due to dangerous road conditions or from speeding. The causes of death in the other incidental cases were cancer (n = 4), acute myocardial infarction (n = 2), drowning (n = 2), pulmonary embolus (n = 1), mesenteric thrombosis (n = 1), sepsis (n = 1), and trauma secondary to a fall (n = 1). No incidental patients had symptoms of CHF.

Morphologic data from the 3 groups of patients with MVP (sudden death, MR/CHF, incidental) are listed in Tables I and II. Representative hearts from each of the 3 groups are illustrated in Figures 1 to 4. Not unexpectedly, patients with MR/CHF had the greatest heart weight (635 ± 140 g) versus hearts of sudden death patients (398 ± 110 g; p ≤0.001) and incidental patients (373 ± 84 g, p ≤0.001). Similarly, the group with MR/CHF had the largest left ventricular cavity diameter (3.7 ± 0.9 cm) versus the group with sudden death (2.4 ± 0.7 cm, p ≤0.001) and incidental MVP (2.3 ± 0.6 cm, p ≤0.001). Left and right atrial sizes of patients with MR/CHF were significantly larger than those of both sudden death and incidental cases (p ≤0.001).

Several characteristics were similar among sudden death and MR/CHF patients but differed from those who died of incidental causes (Tables I and II). The anterior mitral valve leaflets from both sudden death (2.6 ± 0.4 cm) and MR/CHF (2.9 ± 0.6 cm) cases were significantly longer than incidental cases (2.2 ± 0.4 cm, p ≤0.05 versus sudden death and p ≤0.001 versus MR/CHF). Posterior leaflet lengths in sudden death (2.3 ± 0.4 cm) and MR/CHF (2.4 ± 0.4) cases were also greater than incidental (1.8 ± 0.6, p ≤0.05) cases. The mitral and tricuspid annular circumferences in sudden death (12.3 ± 1.9 cm and 12.3 ± 1.2 cm, respectively) and in MR/CHF (13.3 ± 1.6 cm and 13.0 ± 1.2 cm, respectively) cases were significantly larger than those of incidental cases (9.9 ± 1.6 cm and 11.2 ± 2.0 cm, respectively). Furthermore, sudden death patients had greater intermediate scallop thickness (1.8 ± 0.7) of the posterior mitral valve leaflet than did the incidental group (1.2 ± 0.7, p ≤0.05). Endocardial plaque was observed in 80% of sudden death hearts compared with 53% of hearts from incidental cases (p
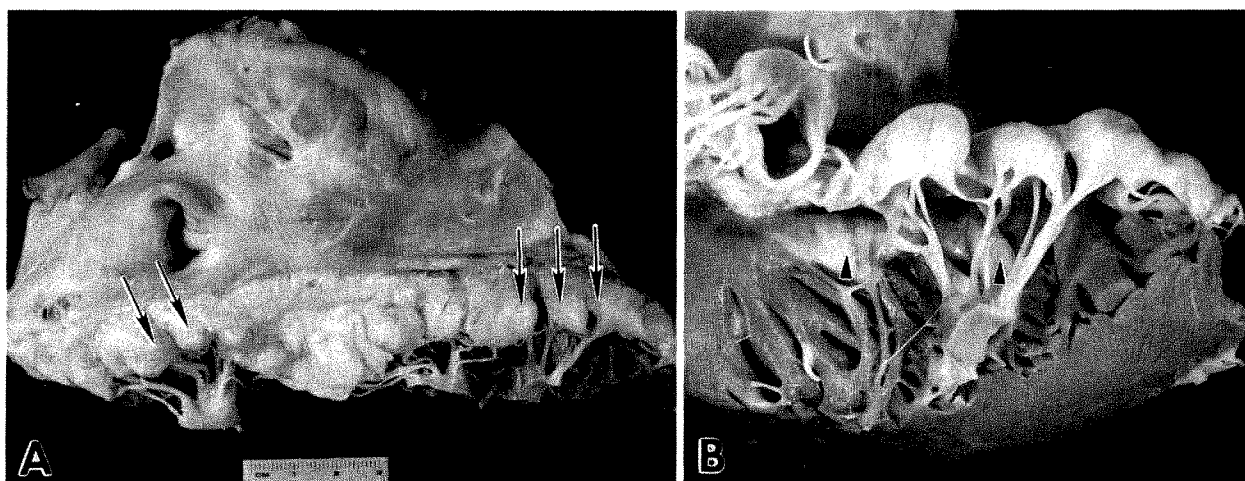
FIGURE 1. A, heart from a 31-year old white woman who collapsed suddenly and died after complaining of acute dyspnea. There was history of mitral valve prolapse and supraventricular arrhythmias. Note markedly redundant and hooded posterior leaflet (arrows). B, the anterior leaflet and a portion of the posteromedial papillary muscle are reflected toward the left atrium to reveal endocardial plaque (arrowheads).
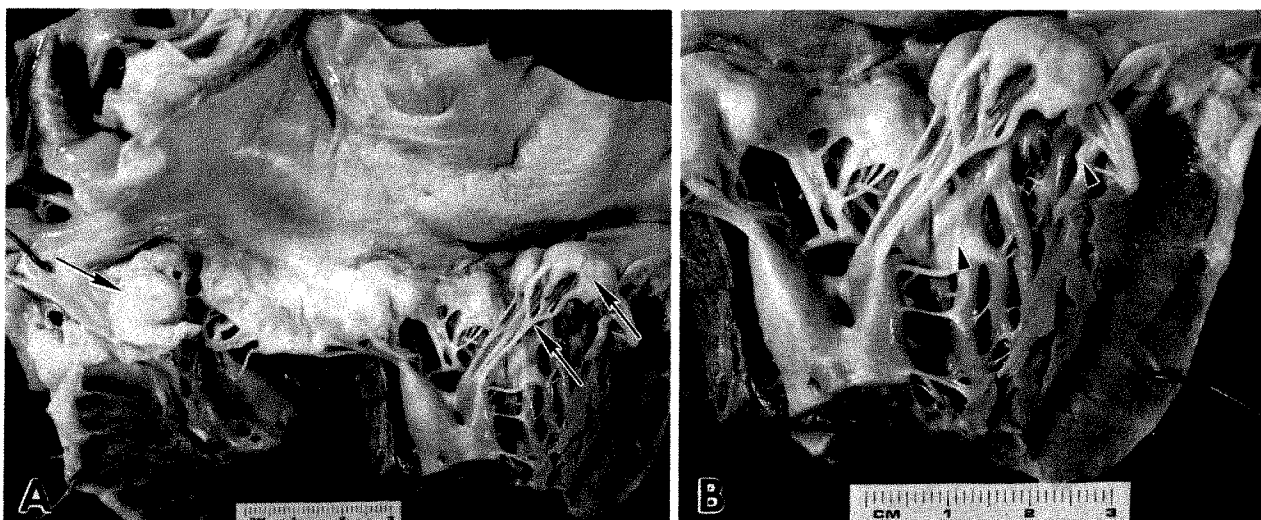
FIGURE 2. A, a 54-year-old white man who died suddenly without any previous cardiac history. Note the elongated and billowing intermediate and posterior scallops of the posterior mitral valve leaflet (arrows). B, close-up view of the posterior leaflet showing elongation of the chordae tendineae and subvalvular endocardial plaque (arrowheads).
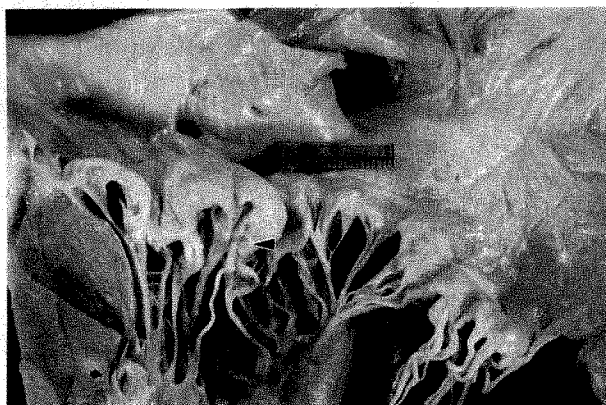
FIGURE 3. A 70-year-old white man with chronic congestive heart failure, severe mitral regurgitation and atrial fibrillation. The mitral leaflet is markedly redundant and hooded with marked elongation of chordal tendineae. A ruptured chorda is present (arrowhead). There is involvement of both the anterior and posterior mitral leaflets.

FIGURE 4. An 18-year-old white woman who died in a motor vehicle accident and was found to have incidental mitral valve prolapse at autopsy. Mild hooding and elongation of the intermediate and anterior scallops of the posterior leaflet are present.

≤0.05), and when present, plaque was more extensive in patients who died suddenly than in those who died from incidental causes (p ≤0.05).

There were no significant differences among the groups with respect to right ventricular thickness, anterior mitral valve leaflet thickness, percent involvement of the anterior leaflet, and thicknesses of the anterior and posterior scallops of the posterior mitral valve leaflet. The histologic characteristics of the sections of the involved valve leaflets consisted of varying grades of expanded spongiosa with extension into the fibrosa, valvular fibrosis, and elastic fiber duplication. There were no significant differences in valve histology among the groups.

DISCUSSION

In a population of patients with MVP studied at autopsy, persons with isolated MVP and sudden death

were significantly younger than patients with MVP associated with MR and CHF and persons in whom MVP was an incidental finding unrelated to the cause of death. Sudden death cases were nearly equally divided among men and women. Several cardiac morphologic features differed among the 3 groups studied. Not unexpectedly, patients with MR and CHF had the greatest heart weight, left and right atrial sizes, and left ventricular cavity size than persons with sudden death and incidental MVP. Importantly, hearts from persons with sudden cardiac death but without significant MR shared certain characteristics with the MR/CHF group and differed from incidental MVP cases. Patients dying suddenly with isolated MVP and patients with MR/CHF had larger mitral and tricuspid annular sizes and greater anterior and posterior leaflet lengths (Figure 5). In sudden death cases, there was increased posterior leaflet intermediate scallop thickness, and endocardial
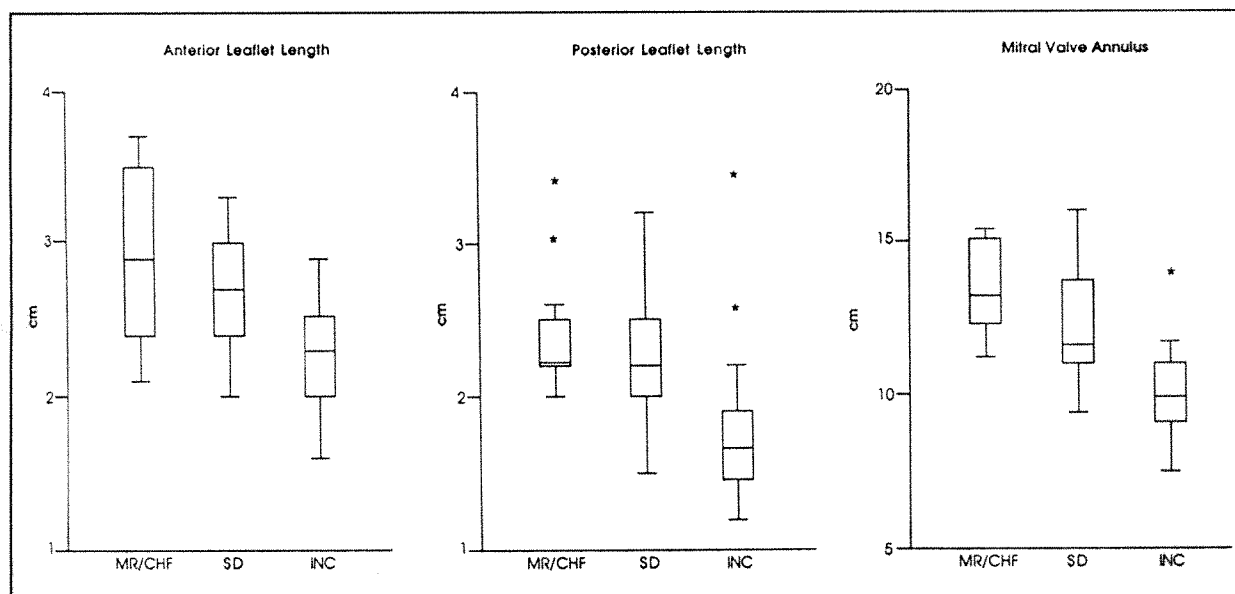
FIGURE 5. Boxplots of data for anterior and posterior leaflet length, and mitral valve annulus circumference in mitral valve prolapse associated with mitral regurgitation and congestive heart failure (MR/CHF), sudden death (SD) and incidental (INC) cases.

plaque was more often present and more extensive versus incidental MVP. Thus, it would appear that the group of hearts from sudden death patients and isolated MVP occupy a middle ground, sharing several valvular characteristics with the MR/CHF group, but more like the incidental group with respect of other nonmitral valvular features such as heart size, wall thickness and cavity dimension. These morphologic differences may be of some clinical relevance because annular size and leaflet thickness and length can be assessed antemortem by echocardiography.[17,18]

While MVP is believed to be benign in most patients, there is evidence from several studies[6,15,19] that complications are not infrequent. In a prospective study by Düren et al[6] of 300 patients with MVP, 100 developed serious complications (ventricular tachycardia, endocarditis, mitral valve surgery, cerebrovascular accidents, sudden death and ventricular fibrillation). The relatively small risk of sudden death must be contrasted with data indicating that patients with isolated MVP may constitute a substantial proportion of patients referred for electrophysiologic testing for malignant ventricular arrhythmias (2 to 17%).[20-22] The morphologic findings in the present autopsy study of MVP are supportive of the clinical data reported by Nishimura et al.[15] They prospectively studied 237 patients with MVP and found 6 cases of sudden death (2.5% of the entire group) consisting of 4 men and 2 women, 3 of whom had a history of ventricular ectopy. In multivariant analysis, echocardiographic evidence of leaflet thickening and redundancy was the only variable associated with sudden death.

Previous autopsy studies of morphologic findings in cases of MVP-associated sudden cardiac death are limited. In a report of 4 persons dying suddenly with MVP, there was marked mitral valve leaflet thickening and billowing.[13] In a recent report by Dollar and Roberts,[16] pathologic cardiac findings at autopsy were studied in a group of patients with MVP. Of 56 patients with MVP there were 15 sudden deaths and 41 with other conditions that were potentially fatal (7 of these had congenital heart disease and were excluded from comparison with sudden death). Sudden death patients were younger at the time of death, were more often women, and had a lower frequency of MR. There were no significant differences in the mitral and tricuspid annular circumferences, anterior and posterior leaflet lengths, or the presence or absence of endocardial plaque. The reasons for the disparities in results in the present study from those of Dollar and Roberts may be due to methodologic differences. The 15 hearts of patients in whom sudden death was attributable to MVP (1 with and 14 without severe MR) were compared with those of 34 patients, 12 of whom had severe MR. In the present study, we separated cases into sudden death (n = 27), MR/CHF (n = 14) and incidental (n = 19) groups and compared each with the other. Also, in the present study, there were nearly twice the number of persons with sudden death and isolated MVP.

The mechanism of sudden death in patients with isolated MVP prolapse is uncertain but is presumed to involve the generation of malignant ventricular tachyarrhythmias.[11,14,23] Endocardial friction lesions have been noted in previous cases of MVP-associated sudden death.[11] In a report by Chesler et al,[12] 12 of 14 hearts from patients with sudden death attributable to MVP had friction lesions.[11] The presence of increased frequency and severity of endocardial plaque (friction lesions) in sudden death patients in the present study is of interest because the myocardium adjacent to these friction lesions may serve as an arrhythmogenic focus. However, the clinical significance of friction lesions is conjectural, and as previously noted, an increased prevalence of endocardial plaques in sudden death cases has not been confirmed in other studies.[16]

Study limitations: This report is a retrospective analysis of 60 autopsy cases of MVP. There were more men than women compared with the increased prevalence of MVP in women in the general population. This may reflect the referral base of our institution. Young adults with unexpected sudden death may be more likely to undergo autopsy than older persons and could produce a selection bias. The cause of death in approximately 40% of the incidental cases was unnatural; it is possible that death in these persons may have been related to their MVP had they lived longer. Although the results indicate that there are differences among hearts from persons with MVP and sudden death compared with those from persons with MR/CHF and incidental MVP, there is some overlap among the groups (Figure 5). Finally, a substantial proportion of sudden death persons were asymptomatic and did not have a premortem diagnosis of MVP. Thus, these persons would presumably remain unidentified even if an improved clinical measurement of risk was available.

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Hemodynamic Evaluation by Doppler Echocardiography of Small (≤21 mm) Prostheses and Bioprostheses in the Aortic Valve Position

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To assess resting hemodynamics of an unselected group of patients with prostheses or bioprostheses sized ≤21 mm implanted into the aortic valve position during a 7-year period, 46 of 50 eligible patients were examined by Doppler echocardiography. The valves were Carpentier-Edwards (CE) supraannular 21 mm (n = 8), Medtronic-Hall (MH) 20 mm (n = 8) and 21 mm (n = 21), and the rest (n = 9) were other valves with only 1 to 3 patients in each group. Gradients, valve areas and dimensionless obstruction indexes (ratio of subvalvular/valvular velocities and velocity time integrals) were compared. By analysis of variance, gradients did not differ significantly between the CE supraannular 21 mm, the MH 20 and 21 mm prostheses (peak/mean 25 ± 8/14 ± 5, 31 ± 13/16 ± 6 and 25 ± 10/13 ± 5 mm Hg; p = not significant). Only 2 patients had a mean gradient >25 mm Hg. The valve area was slightly larger for the MH 21 mm group compared with the CE supraannular 21 mm group (1.34 ± 0.15 vs 1.16 ± 0.14 cm², p <0.05). The dimensionless obstruction indexes did not differ (CE supraannular 21 mm 0.36 ± 0.07/0.40 ± 0.07 (velocities/velocity time integrals), MH 20 mm 0.40 ± 0.12/0.47 ± 0.12, MH 21 mm 0.38 ± 0.05/0.44 ± 0.06; p = not significant). An inverse relation was demonstrated between the left ventricular outflow tract diameter and the subvalvular velocities (r = −0.60, p <0.001), thus emphasizing the necessity of making a correction for prevalvular velocities when applying the Bernoulli equation in calculating gradients across small aortic valve prostheses. It is concluded that acceptable resting hemodynamics are obtained with the CE supraannular 21 mm, the MH 20 and 21 mm prostheses in the narrow aortic root. The moderate obstruction caused by the prostheses is not likely to be a limiting factor for the hemodynamic capacity of these patients.

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The hemodynamic properties of small aortic valve prostheses are questioned and the management of the narrow aortic root remains controversial. An alternative to a small prosthesis is root enlargement that may allow insertion of a larger valve,[1-3] but this will prolong the surgical procedure and may increase the operative risk.[4] Patients presenting with a narrow root are often elderly, and a bioprosthesis would be preferable. It has been claimed that small-sized bioprostheses should be avoided because unfavorable gradients may result.[5] The hemodynamic performance of different types of small aortic prostheses and bioprostheses are therefore of clinical interest because the results may influence decision making in patients with a narrow aortic root. With Doppler echocardiography an accurate noninvasive assessment of the prosthesis function is possible. Mean gradients, cardiac output and valve area estimates have been shown to correlate well with invasive measurements,[6-10] and regurgitations can be detected and semiquantified.[7,11,12] Left ventricular outflow tract obstructions may occur, especially in patients with a narrow aortic annulus,[13] and with Doppler ultrasound both the level and the degree of outflow tract obstructions may be established.[14,15] To assess resting hemodynamics in an unselected group of patients with small aortic valve prostheses, all patients receiving a ≤21 mm prosthesis or bioprosthesis at our institution were considered for Doppler echocardiographic study.

METHODS

Patients: In the period from 1983 to 1989 58 prostheses (43 mechanical, 15 biological) with an external diameter ≤21 mm were implanted into the aortic valve position. There were 2 early and 5 late deaths. One patient with a Medtronic-Hall (MH) 21 mm prosthesis was admitted with heart failure 5.5 months after surgery. A thrombotic obstruction was diagnosed by Doppler echocardiography and at reoperation a thrombus was removed. Thus, a total of 50 patients were eligible for the present study. Because of age and geographic considerations 4 patients were not contacted. The remaining 46 (92% of those eligible) all underwent Doppler echocardiographic study.

There were 44 women and 2 men, mean age 66 years (range 23 to 82) and mean body surface area 1.65 ± 0.12 m² (range 1.34 to 1.91). The preoperative diagnosis was pure or predominant stenosis in 44 and pure regurgitation in 2 patients. The valves were 8 Carpentier-Edwards (CE) supraannular 21 mm, 8 MH 20 and

TABLE I Peak and Mean Gradients, Valve Areas and Dimensionless Obstruction Indexes for Different Valve Types

Valve Type (mm)	No.	Peak (mm Hg)	Mean (mm Hg)	PVA₁ (cm²)	PVA₂ (cm²)	V_{lvot}/V_{valv}	VTI_{lvot}/VTI_{valv}
CE porcine (21)	2	22 ± 4	12 ± 4	1.13 ± 0.27	1.31 ± 0.36	0.41 ± 0.04	0.48 ± 0.06
		18–26	8–15	0.86–1.39	0.95–1.67	0.38–0.44	0.42–0.53
CE pericardial (21)	2	20	12	1.26 ± 0.12	1.30 ± 0.07	0.40 ± 0.04	0.41 ± 0.02
				1.14–1.37	1.23–1.37	0.36–0.43	0.39–0.43
CE supraannular (21)	8	25 ± 8	14 ± 5	1.06 ± 0.16	1.16 ± 0.14*	0.36 ± 0.07	0.40 ± 0.07
		14–40	7–23	0.86–1.31	0.99–1.42	0.27–0.47	0.32–0.52
MH (20)	6	31 ± 13	16 ± 6	1.06 ± 0.22	1.19 ± 0.21	0.42 ± 0.12	0.47 ± 0.12
		11–54	6–25	0.83–1.50	0.95–1.59	0.29–0.66	0.33–0.70
MH (21)	19	25 ± 10	13 ± 5	1.17 ± 0.13	1.34 ± 0.15*	0.38 ± 0.05	0.44 ± 0.06
		14–60	7–31	0.91–1.38	1.03–1.57	0.28–0.46	0.32–0.55
Sorin (21)	3	31 ± 3	17 ± 1	1.07 ± 0.17	1.18 ± 0.16	0.40 ± 0.07	0.44 ± 0.08
		28–35	16–19	0.92–1.30	1.01–1.39	0.29–0.46	0.32–0.51
Duromedics (19)	1	51	27	0.84	1.01	0.33	0.40
Duromedics (21)	1	19	10	1.28	1.40	0.41	0.45

*p <0.05 when comparing Carpentier-Edwards supraannular 21 mm with Medtronic-Hall 21 mm prostheses (standard continuity equation).
Values are mean ± SD.
From the total group of 46 patients, 2 with a Medtronic-Hall 20 and 1 with a Medtronic-Hall 21 mm valve prosthesis were excluded from the analysis because of a history of thromboembolism, and 1 patient with a Medtronic-Hall 21 mm valve was excluded because of a perivalvular leak grade 3. Thus, the number of patients included in this analyses is 42.
CE = Carpentier-Edwards; MH = Medtronic-Hall; PVA₁ = prosthetic valve area (simplified continuity equation); PVA₂ = prosthetic valve area (standard continuity equation); V_{lvot} = velocity in left ventricular outflow tract; V_{valv} = velocity across prosthesis; VTI_{lvot} = velocity time integral in left ventricular outflow tract; VTI_{valv} = velocity time integral across prosthesis.

21 MH 21 mm, and the rest (n = 9) were other valves with only 1 to 3 patients in each group (Table I).

The MH 20 and 21 mm prostheses are identical except for a thinner sewing ring in the 20 mm valve in order to allow insertion in even smaller roots. Mean time from surgery to the Doppler echocardiographic study was 2.2 years. Three patients, all with a CE supraannular 21 mm valve, were examined 1 to 2 weeks postoperatively. In all other patients the time interval from surgery was ≥3 months with a maximum of 38 months in the bioprosthesis group. To reduce the risk of including patients with dysfunctioning prostheses in the comparison between valve types, 3 patients (2 MH 20 and 1 MH 21 mm) with a history of thromboembolic episodes were excluded from the analysis of gradients and valve area.

Doppler echocardiography: An Irex Meridian or Vingmed CFM 700 ultrasound system with a 3.0 MHz transducer for imaging and 2.0 or 2.5 MHz for Doppler recordings was used.

Leaks: Prosthetic leaks were assessed with color flow using the Vingmed CFM 700. Regurgitations were graded on a scale from 0 to 4. Tiny regurgitant jets confined within the left ventricular outflow tract were graded 1+. With a somewhat larger origin and jet area, but with the jet still not extending to the tip of the anterior mitral valve leaflet, the leak was graded 2+, and with extension beyond the leaflet tip without reaching the apex 3+. No one had 4+ regurgitation. To judge the regurgitation as valvular or perivalvular, several imaging planes were used, and it was categorized as perivalvular if the jet was seen to originate outside the valve ring.

Pressure decrease: Velocities across the prostheses were recorded using continuous-wave Doppler from apical, suprasternal and right parasternal positions. From the highest velocities obtained, the pressure decrease was calculated using the Bernoulli equation with correction for prevalvular velocities: Pressure decrease = $4(V_{valv}^2 - V_{lvot}^2)$ where V_{valv} = velocity across prosthesis and V_{lvot} = left ventricular outflow tract velocity.[16]

Intraventricular and left ventricular outflow tract velocities: Pulsed Doppler was used to search for increased velocities within the left ventricle. The sample volume was moved stepwise from the apex up through the left ventricle to the level of the prosthesis. Left ventricular outflow tract velocities were recorded with the sample volume positioned just below the prosthesis.

Cardiac output, prosthesis valve area: From the parasternal long-axis view the inner left ventricular outflow tract diameter was measured just below the prosthesis (Figure 1). Cardiac output (CO) was calculated from the formula CO = $(D/2)^2 \times \pi \times VTI_{lvot} \times HR$, where D = subvalvular diameter, VTI_{lvot} = velocity time integral in the outflow tract and HR = heart rate. With sinus rhythm at least 3, and with atrial fibrillation at least 10 consecutive beats were averaged. The prosthetic valve area (PVA) was calculated using both the standard continuity equation — PVA = SV/VTI_{valv} where SV is stroke volume and VTI_{valv} is velocity time integral across the prosthesis, and the simplified equation — PVA = $A_{lvot} \times V_{lvot}/V_{valv}$ where A_{lvot} and V_{lvot} is the left ventricular outflow tract area and maximal velocity respectively, and V_{valv} is the maximal velocity across the prosthesis.[17,18]

Dimensionless obstruction index: By eliminating the subvalvular area from the continuity equation,[10] the dimensionless obstruction index is obtained. The ratios V_{lvot}/V_{valv} and VTI_{lvot}/VTI_{valv} were calculated and compared for the different valve types.

Statistical analysis: Continuous variables are expressed as mean ± SD. Means of 2 groups were compared using an unpaired t test. With multiple comparison, analysis of variance followed by the Student-Newman-Keuls test was used. Statistical analysis of the association between variables was performed using linear regression analysis. A p value <0.05 was considered

significant. Reproducibility is expressed as the 95% limits of agreement between pairs of measurements as described by Bland and Altmann.[19]

RESULTS

Adequate Doppler recordings were obtained in all patients. In 1 patient (MH 21 mm) the sewing ring diameter was used to calculate the outflow tract area as the echocardiographic window did not allow for a subvalvular diameter measurement.

Leaks: One patient with an MH 21 mm prosthesis implanted during ongoing endocarditis had a 3+ perivalvular leak and was excluded from the analysis of pressure decrease and effective orifice area. In 4 patients, all with an MH 21 mm prosthesis, perivalvular leaks grade 1 to 2 were diagnosed. Cardiac output in

these 4 was not increased compared with the rest of the MH 21 mm group (4.82 ± 0.44 vs 4.94 ± 0.87 liters/min, p = NS), supporting the judgment of the regurgitations as being mild. Two patients with a bioprosthesis had a grade 1 perivalvular leak.

Pressure decrease: The highest velocities were obtained from the apex in 27 of 34 mechanical valves (78%) and in 10 of 12 bioprostheses (83%). Table I lists the gradients across the different valves, and the variation within each valve type is demonstrated in Figure 2. Only 2 patients had a mean gradient >25 mm Hg. Because of the small number of other valve types, only the CE supraannular 21 mm and the MH 20 and 21 mm prostheses were compared statistically. By analysis of variance no statistically significant differences in gradients were found between these 3 groups.
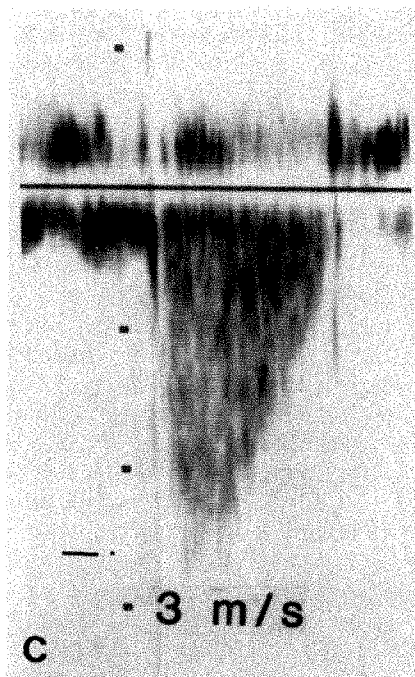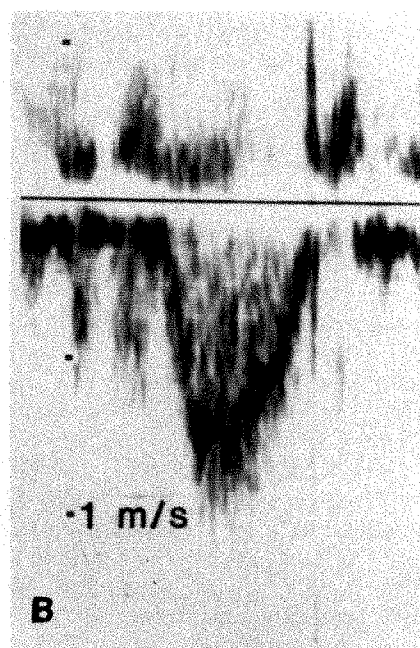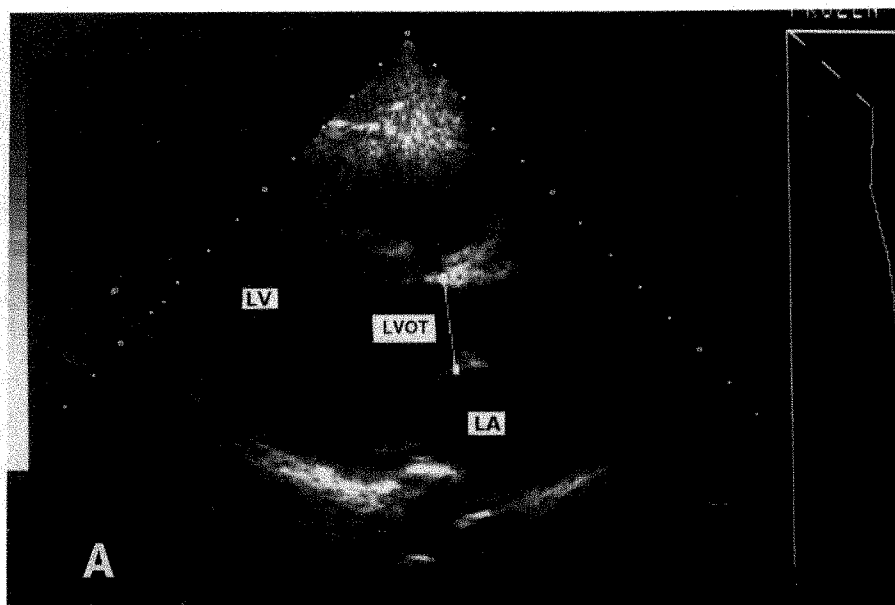
FIGURE 1. Measurement of left ventricular outflow tract (LVOT) diameter (A), pulsed Doppler recording in the left ventricular outflow tract close to the prosthesis (B), and continuous-wave Doppler recording of velocities through the prosthesis (C). LA = left atrium; LV = left ventricle.

TABLE II Comparison of Left Ventricular Outflow Tract Measurements in
Carpentier-Edwards Supraannular 21 mm, Medtronic-Hall 20 and 21 mm Valves

Valve Type (mm)	No.	D_{lvot} (cm)	V_{lvot} (m/s)	VTI_{lvot}	CO (liters/min)
CE supraannular (21)	8	1.94 ± 0.1	0.95 ± 0.16	19.2 ± 3.0	4.68 ± 0.90
		1.7–2.0	0.61–1.16	13.8–24.4	3.48–6.52
MH (20)	8	1.80 ± 0.1*	1.23 ± 0.22*	30.3 ± 3.5*	5.19 ± 1.04
		1.7–2.0	0.93–1.61	25.7–34.9	3.84–7.37
MH (21)	20	1.98 ± 0.11	1.02 ± 0.16	24.5 ± 3.7	4.94 ± 0.87
		1.7–2.1	0.63–1.28	16.4–31.3	3.33–6.66

*Medtronic-Hall 20 mm group differs significantly from both the Carpentier-Edwards supraannular and Medtronic-Hall 21 mm groups by the Student-Newman-Keuls procedure.
Values are mean ± SD.
CO = cardiac output; D_{lvot} = diameter of left ventricular outflow tract; other abbreviations as in Table I.

FIGURE 2. Peak *(top)* and mean *(bottom)* gradients for different valve types. CE = Carpentier-Edwards; CES = Carpentier-Edwards supraannular; DM = Duromedics; MH = Medtronic-Hall; SO = Sorin.
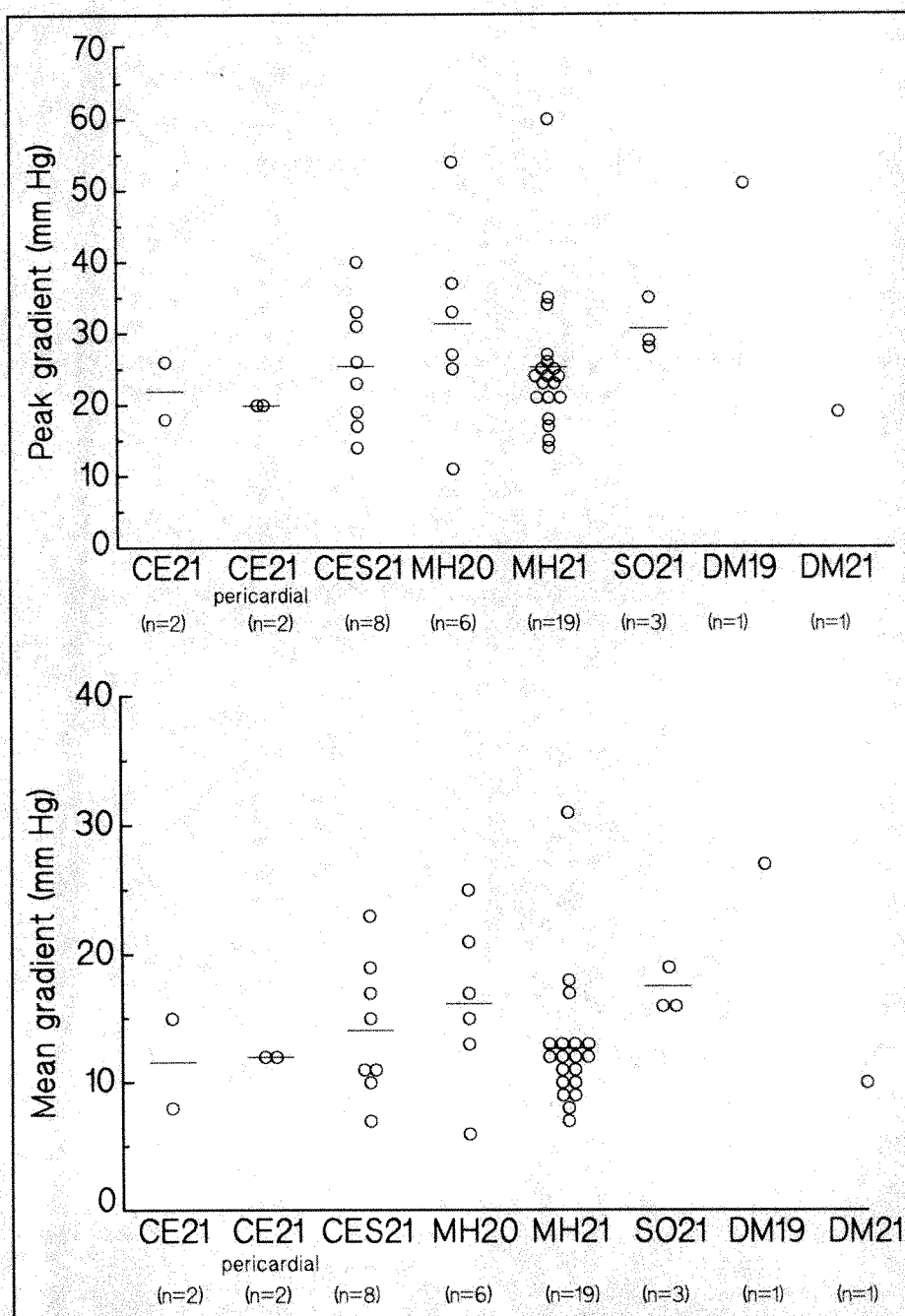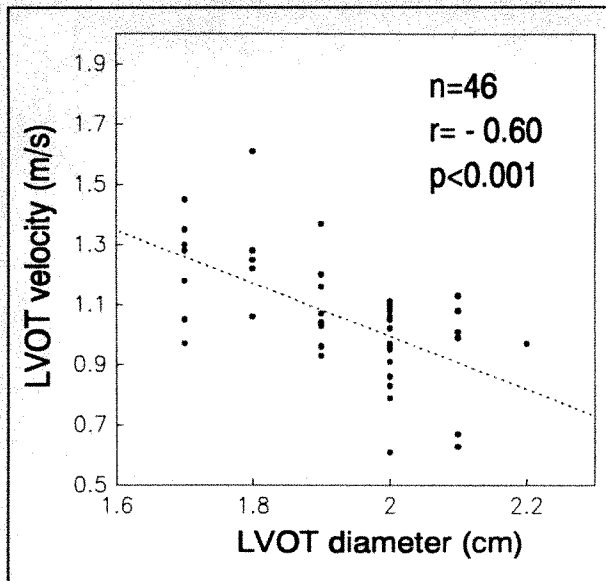
FIGURE 3. A negative correlation was demonstrated between the left ventricular outflow tract (LVOT) diameter and velocities.

Subvalvular diameters and velocities (Table II): The subvalvular diameter was significantly smaller in the MH 20 mm group, with an average difference of 0.18 cm between the MH 20 and 21 mm prostheses. The subvalvular velocities and velocity time integrals were higher in the MH 20 mm group compared with the CE supraannular and the MH 21 mm groups. A negative correlation was found between the subvalvular diameters and outflow tract velocities (Figure 3). The highest subvalvular velocity recorded was 1.61 m/s.

Prosthetic valve area, dimensionless obstruction index (Table I): The valve areas calculated by the simpli-

fied and standard continuity equation were highly correlated (Figure 4). With the standard continuity equation, a significantly smaller area was found for the CE supraannular valves than for the MH 21 mm group. When comparing the MH 20 and 21 mm valves, areas tended to be lower for the 20 mm group, although this did not reach statistical significance (p = 0.06). The dimensionless obstruction indexes did not differ among the groups (Table I).

Intraventricular velocities: Six patients (13%) had intraventricular velocities >1.5 m/s and a characteristic pattern of the velocity curve with the highest velocities at end systole (Figure 5). These velocities were usually recorded at the midventricular level, and were not considered to represent left ventricular outflow tract obstructions. The highest midventricular velocity measured was 3.8 m/s, corresponding to an intraventricular gradient of 57 mm Hg. The patients with this flow pattern did not differ with respect to age or time interval from surgery. Heart rate tended to be higher (77 ± 12 vs 68 ± 11 beats/min, p = 0.07) and left ventricular ejection time shorter (281 ± 39 vs 311 ± 35 m/s, p = 0.06) in these patients, indicating a somewhat hyperdynamic circulatory state.

Reproducibility: In a recent study we found the subvalvular diameter measurement to be a major source of variance in calculation of stroke volume and orifice area in patients with aortic valve prostheses (Rossvoll, unpublished data). In the present study the diameter was measured independently by 2 observers in 15 randomly selected patients. The difference in diameter recordings was within 2 mm in 13 of 15 patients (87%), with identical measurements in 6. To assess reproducibility of valve area measurements, 9 patients were reexamined within 1 to 14 months. The upper and lower limits of agreement were 0.34/−0.14 cm² and 0.32/−0.16 cm²
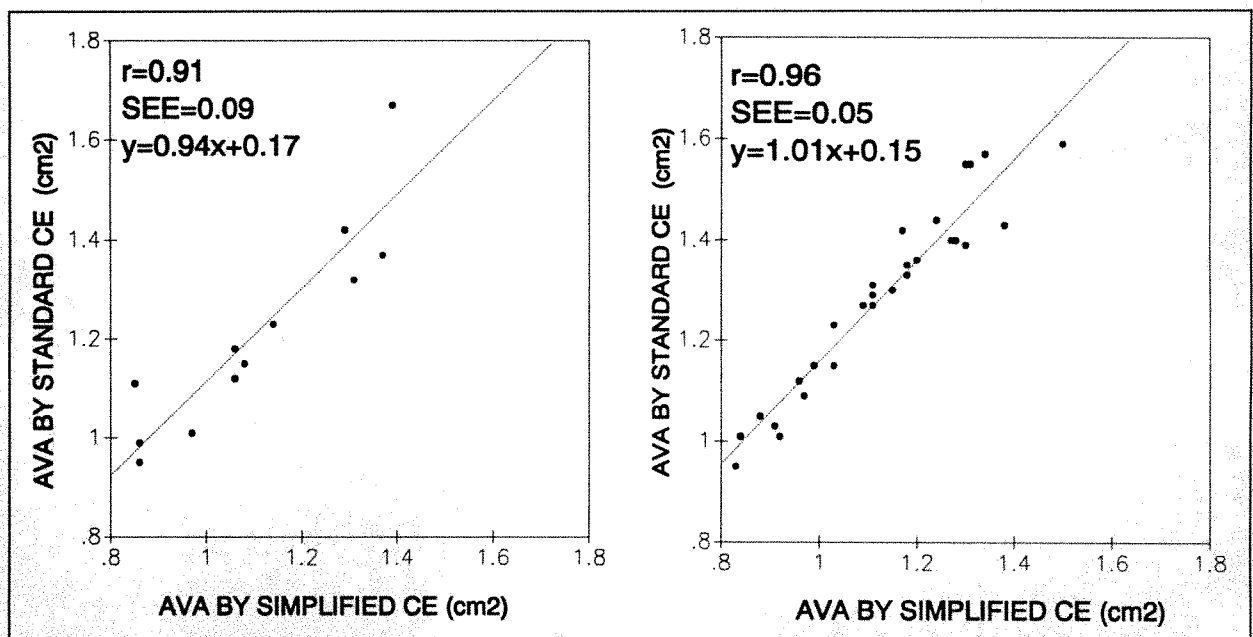
FIGURE 4. The prosthetic aortic valve areas (AVA) obtained with the simplified and the standard continuity equation (CE) were highly correlated for both bioprostheses (left) and mechanical valves (right).

with the simplified and standard continuity equation, respectively. The limits of agreement for the dimensionless obstruction index were 0.09/−0.07 (velocities) and 0.08/−0.03 (velocity time integrals).

DISCUSSION

Resting hemodynamics of small (≤21 mm) aortic valve prostheses and bioprostheses are well assessed by Doppler echocardiography. No patient was excluded because of technically inadequate recordings. The predominant characteristics of the patients studied (female sex, small body surface area) are considered representative for an unselected group of patients with a small aortic prosthesis. A similar profile of patients with a narrow aortic annulus is described by others.[20,21]

Perivalvular leaks: Perivalvular leaks were diagnosed in 7 patients (15%). Except for the patient with a 3+ leak after reoperation during endocarditis, the leaks were assessed as minor and without hemodynamic significance. It is noteworthy that no case of pathologic leak was found with the MH 20 mm prosthesis indicating that the thinner sewing ring does not predispose for perivalvular leaks. To our knowledge there is no earlier report presenting noninvasive hemodynamic data of this prosthesis.

Pressure decrease: The pressure decrease recorded across these ≤21 mm valves was acceptable; only 2 patients had a mean gradient >25 mm Hg. Earlier reports on hemodynamic properties of small aortic valve prostheses are mostly based on invasive studies. The average mean gradient of 13 mm Hg across the MH 21 mm prostheses in this study corresponds well with an average mean gradient of 12 mm Hg reported from catheterization of 9 patients with this prosthesis.[22] A mean gradient of 19 mm Hg is reported after catheterization of 16 patients with a 21 mm CE pericardial valve.[23] In our study the CE valves had favorable gradients (Figure 2), indicating that they provide an acceptable alternative in the narrow aortic annulus when a tissue valve is desired. There are few reports on noninvasively obtained gradients across 21 mm prosthetic valves. After a review of published reports, Reisner and Meltzer[24] reported noninvasive data of 25 St. Jude Medical, 5 Bjørk-Shiley and 7 CE pericardial 21 mm valves. The average peak and mean gradients ranged from 27.3 to 30.5 and from 14.4 to 16.0 mm Hg, respectively. The results in our study are in the same ranges.

Prosthetic valve area: An excellent correlation between valve areas obtained with the standard and simplified continuity equation has been described for bioprostheses.[25] According to our study the 2 methods relate similarly in mechanical valves (Figure 4). Earlier reports on prosthetic valve areas are mostly based on invasive measurements using the Gorlin formula,[26] but the adequacy of this formula in predicting prosthetic valve area is questioned.[27] So far there is a paucity of noninvasive data on valve areas in ≤21 mm aortic valve prostheses and bioprostheses. Similar to our results an area of 1.39 ± 0.55 cm^2 is reported for the 21 mm Ionescu-Shiley pericardial valve,[28] and 1.02 ± 0.10 cm^2 for the 21 mm Medtronic-Intact bioprosthesis.[25] In vitro studies have demonstrated a progressive opening of the CE bioprostheses with increasing flow rates.[23] The smaller orifice area calculated for the CE compared to the MH 21 mm valves in this study could therefore be attributed to a lower stroke volume in the former group (57 ± 12 vs 75 ± 12 ml, p <0.001). Although the MH 20 and 21 mm prostheses have identical inner orifice areas, valve area tended to be lower and gradients higher for the 20 mm valves. The discrepancy between the 1 mm difference in external diameter and the difference of 1.8 mm in subvalvular diameter in the 2 groups could indicate that the 20 mm prostheses are inserted in roots that, relative to the prosthesis size, are narrower than the roots where a 21 mm prosthesis is inserted. This could result in a more oblique positioning in the aortic annulus, and the orientation of the major orifice could be less than optimal precluding an effective utilization of the prosthesis area.

Dimensionless obstruction index: This parameter did not significantly differ between the groups (Table I). With this index, the sometimes difficult and time-

FIGURE 5. Increased midventricular velocity recorded close to the septum. Note the typical shape of the curve with the highest velocity occurring at the end of systole.
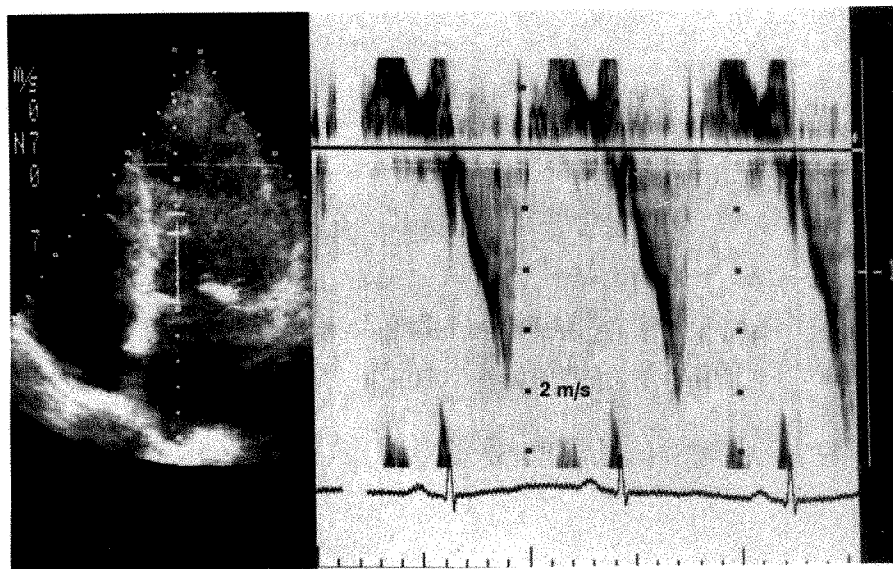
consuming diameter measurement and the inaccuracies it may introduce are omitted. To our knowledge this index has not been reported earlier for ≤21 mm aortic valve prostheses, but this parameter may prove valuable in the follow-up of patients with aortic valve prostheses and should be further evaluated.

Subvalvular velocities: With decreasing left ventricular outflow tract diameter, increasing subvalvular velocities were found (Figure 3). This finding emphasizes the necessity of making correction for prevalvular velocities when applying the Bernoulli equation in aortic valve prostheses.[16] Otherwise gradients will be overestimated to a varying degree with the largest overestimation occurring in patients with a narrow outflow tract. In our study this is illustrated with the MH 20 mm valve. Without correction the calculated peak and mean gradients across this valve would on average have been 6 (19%) and 4 (25%) mm Hg higher than the values listed in Table I. Occasionally a subvalvular obstruction may occur after valve replacement in a narrow aortic root.[13] The highest outflow tract velocity recorded in this study was 1.61 m/s, indicating no significant subvalvular obstruction in any of these patients.

Clinical implications: Resting hemodynamics in an unselected group of ≤21 mm aortic valve prostheses and bioprostheses implanted during a 7-year period were acceptable. The moderate obstruction caused by the prostheses is not likely to be a limiting factor for the functional capacity in these patients. When assessing function of prosthetic aortic valves noninvasively, subvalvular velocities should routinely be recorded; otherwise the transprosthetic gradient will be overestimated to a varying degree.

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Usefulness of Transesophageal Echocardiography in Evaluation of Paracardiac Neoplastic Masses

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Mediastinal paracardiac tumors may cause both cardiovascular complications and problems in differential diagnosis of cardiac diseases. Transesophageal echocardiography (TEE) may give an additional new window to mediastinal neoplasms, but only a few studies have been reported. TEE was performed in 70 patients with paracardiac neoplastic masses. The procedure was indicated to solve particular clinical problems in 20 patients, and as a prospective study on 50 unselected patients with mediastinal neoplasms. Twenty-three patients underwent follow-up studies; a total of 101 echocardiograms were recorded. The procedure was tolerated well or very well by most patients, and provided additional anatomic or hemodynamic data in every patient in group a and in 45 of 50 in group b. The additional data were relevant for clinical management in 14 of 20 patients in group a, and in 3 of 45 in group b. Based on the results of this study, TEE is useful in association with other radiologic techniques in patients with paracardiac neoplasms. As an imaging technique, it may represent a reliable alternative to computed tomography whenever the latter is not feasible.

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Secondary cardiac involvement by neoplastic disease has been an emerging field of interest in recent years.[1-5] The cardiologist can be involved in the management of patients with neoplastic paracardiac masses for several reasons: (1) The mass compresses or infiltrates cardiovascular structures. (2) The presenting signs and symptoms of the tumor mimic a cardiovascular disease. (3) The patient must undergo cardiotoxic oncologic therapy.[5-20] Furthermore, when mediastinal abnormalities are detected at a routine chest x-ray, the difference between vascular and nonvascular lesions may be difficult to diagnose.[21,22] Conventional transthoracic 2-dimensional echocardiography has been successfully used in these situations.[1,3,4,9-11,14,15,18,22-25] In some cases, however, it can give incomplete information because of a poor acoustic window. In these cases, transesophageal echocardiography (TEE) may give a more complete imaging approach to both mass and heart. In this article we describe our experience with 70 patients diagnosed with neoplastic paracardiac masses who were studied by TEE in addition to other imaging techniques.

METHODS

Patients: TEE was recommended for 75 consecutive patients referred to us for transthoracic echocardiography for the following reasons: (1) to better define unsolved clinical problems related to the presence of a mediastinal neoplasm (15 patients); (2) to study the possibilities of TEE in the staging of neoplastic paracardiac masses (56 patients); and (3) to explain an abnormal chest x-ray finding (in 4 patients [3 had no previous history of neoplastic disease and 1 had undergone complete resection of renal cancer 9 months earlier]; all patients eventually had a paracardiac neoplasm diagnosed). All patients underwent transthoracic echocardiography before TEE.

Three patients refused the examination, and 2 were unable to tolerate the procedure because of severe vomiting. TEE was then performed on 70 patients (35 men and 35 women, aged 15 to 75 years, mean 36). Twenty-six patients had non-Hodgkin's lymphoma, 23 Hodgkin's disease, 6 sarcoma and 15 other tumors. Twenty-three patients underwent repeat TEE after medical or radiation therapy treatments: in all, 101 TEE examinations were performed. The clinical characteristics of the patients and the need for TEE are summarized in Table I.

We used commercially available equipment: Aloka SSD860 and SSD870 with 2.5 and 3.5 MHz phased-

TABLE I Clinical Characteristics of the Study Group	
	No. of Pts.
Types of neoplasms	
Non-Hodgkin's lymphoma	26
Hodgkin's disease	23
Sarcoma	6
Lung carcinoma	4
Breast carcinoma	2
Neuroblastoma	2
Teratocarcinoma	1
Renal cancer	1
Chronic lymphatic leukemia	1
Thymoma	1
Angioma	1
Unknown	2
Symptoms	
Superior vena cava syndrome	8
Cough	9
Dyspnea	13
Cough and dyspnea	3
No symptoms	68

array transthoracic transducers and different transesophageal single-plane and biplane transducers — UST 5229, UST 5228, UST 5233-5. Local anesthesia was obtained with spray lidocaine or with a tetracaine tablet. Whenever necessary, oral dihydrocodeine was administered to prevent coughing, intravenous diazepam to reduce anxiety, and the antisialogogue glycopyrronium bromide and a mechanical vacuum aspirator. Patients fasted for ≥8 hours before the procedure. The left lateral decubitus position was used for most patients. Nine patients required a sitting position to avoid coughing. One patient with abdominal pain was able to lie in the right lateral decubitus position only. The probe, introduced by a trained physician, was gently pushed into the stomach first to obtain transgastric sections, then slowly withdrawn to obtain all the standard sections described by Seward et al.[25] We also tried to record the color and pulsed Doppler signal of atrioventricular and arterial valves, both venae cavae, pulmonary veins and right and left atrial appendages. Additionally, the probe was rotated clockwise and counterclockwise every 2 to 3 cm to study the descending thoracic aorta and the mediastinal mass.

RESULTS

Procedural problems: Of the 101 procedures performed, 47 were tolerated very well, 39 well, 8 were slightly unpleasant and 7 fairly unpleasant. The procedure had to be interrupted only in 2 patients because of vomiting (both patients had been recently treated with chemotherapy). The main complaints were nausea during the passage of the transducer through the pharynx, esophageal pain and coughing or mild breathlessness. Patients with superior vena cava syndrome tolerated TEE better while in a sitting position and taking dihydrocodeine. Nausea was observed more often in patients taking chemotherapy or those who were very anxious. Those who complained of esophageal pain were mostly patients (1) previously treated with mediastinal radiation therapy; (2) with esophageal compression; and (3)

with a mass in the superior mediastinum, in whom the probe was kept longer in the upper part of the esophagus. Mild breathlessness was a complaint of the first patients examined, in whom TEE was performed with the ultrasound transducer UST 5229, and of 2 patients with lymphoma involving the oropharynx. With the newer transducers UST 5228 and UST 5233-5, characterized by a smaller size and an oval shape, the procedure was better tolerated. Twenty-six patients underwent fiberoptic gastroscopy a few days before or after TEE. Compared with gastroscopy, 3 patients described TEE as more unpleasant, 9 as similar and 14 as more tolerable. Three additional patients, who were unable to undergo gastroscopy because of coughing and vomiting, tolerated TEE quite well. The most important transesophageal echocardiographic sections, described by Seward et al,[25] were obtained in 92 of the 101 examinations. In 2 patients who had a mass compressing the esophagus, only the base of the heart and the surrounding mass could be visualized. In 7 patients who did not tolerate the procedure well, the test was restricted to the sections most relevant to the assessment of the clinical problem.

The procedure lasted 5 to 48 minutes (mean 23), usually 10 to 20 minutes longer than the conventional TEE performed in our laboratory. This was due mainly to the time spent carefully evaluating the possibility of neoplastic masses surrounding, compressing or infiltrating the intrathoracic vessels, and assessing the infiltration of the pericardium. Furthermore, the presence of the mass in some cases distorted the normal relationships of the cardiovascular structures, leading to additional difficulties in orientation.

Thirty-one procedures were performed with a single-plane transducer and 70 with the biplane transducer UST 5233-5. The biplane probe allowed for an easier and more complete visualization of some structures (the superior vena cava, right ventricular outflow tract, left and right atrial appendages, posterior left atrial wall, descending thoracic aorta and pulmonary trunk). The biplane transducer appeared to be particularly useful in follow-up studies in order to assess the complete disappearance of the mass.

Information obtained by transesophageal echocardiography: TEE allowed better visualization of the mass, cardiac chambers and great vessels than did transthoracic echocardiography in 68 of 101 examinations. The neoplastic mass was correctly identified in all but 1 patient with Hodgkin's disease with mediastinal lymph nodes smaller than 2.5 cm. In 2 patients the neoplastic mass was limited to the superior mediastinum: in these patients complete TEE imaging of the mass was difficult because the manipulation of the transducer close to the pharynx was particularly unpleasant for them.

Most of the patients underwent computed tomography (CT) within 2 weeks of TEE. In 7 of our 70 patients CT could not be performed because of severe orthopnea or the need for emergency chemotherapeutic treatment; 1 patient required general anesthesia because of severe claustrophobia; in 5 additional patients the data obtained by CT were limited by the patients'
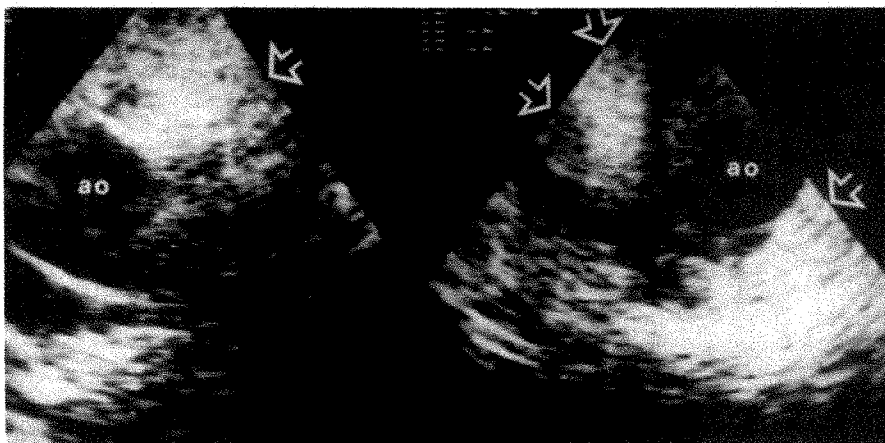
FIGURE 1. A 49-year-old man without previous cardiovascular disease had been complaining of cough and mild effort dyspnea for 2 months. A standard chest x-ray showed a cardiac silhouette with enlarged second arch. This abnormality was considered possibly of vascular origin. Before performing other radiologic investigations, the patient underwent echocardiographic examination. Transthoracic echocardiography did not show any abnormality. Transesophageal echocardiography revealed an echogenic mass surrounding the descending thoracic aorta (ao) from the aortic arch (*left*) to the diaphragm (*right*). The mass was supposed to be a neoplasm involving the periaortic lymph nodes. Computed tomography and mediastinoscopy were soon performed, confirming the echocardiographic data. The histologic diagnosis was non-Hodgkin's lymphoma.
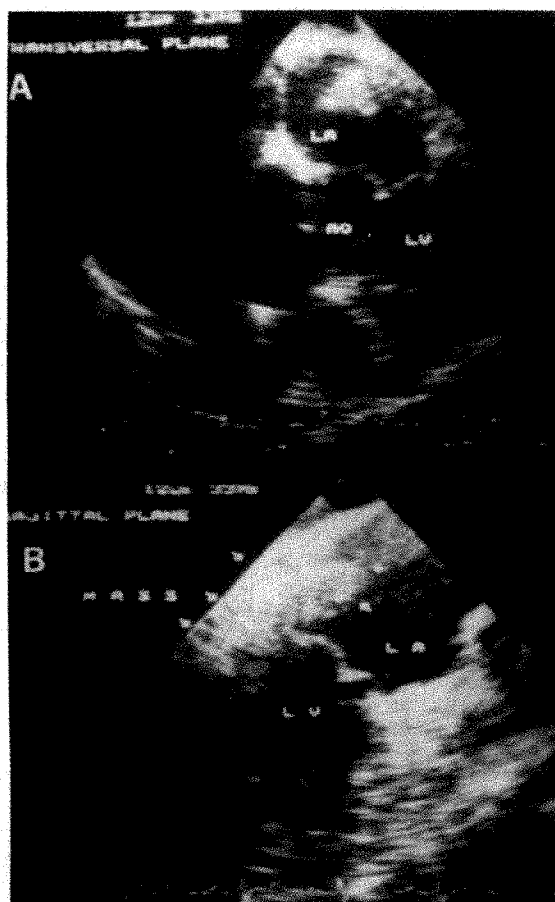
FIGURE 2. This 72-year-old man, affected by non-Hodgkin's lymphoma, was prospectively evaluated by echocardiography in order to assess the relation between the mediastinal mass and the cardiovascular structures. Both computed tomography and transthoracic echocardiography showed a posterior mass in close contact with the left atrium (LA). Transesophageal echocardiography showed a mobile mass within the left atrium, but in the transverse planes the relationships with the paracardiac mass were not clear (*A*). Using the sagittal plane, the infiltration of the posterior atrial wall and the continuity between paracardiac and intracardiac mass were demonstrated (*B*). AO = aorta; LV = left ventricle.

hypersensitivity to iodine contrast media. TEE and CT data were then comparable in 58 cases. In 14 of 58 cases the anatomic data (site, size of the mass, cardiovascular infiltration) obtained by TEE fully corresponded to those obtained by CT. In 3 of these cases TEE, performed in order to explain an abnormal chest x-ray, detected a mediastinal mass later confirmed by CT (Figure 1). One patient had a superior vena cava neoplasm not evident at CT but only at magnetic resonance imaging and at TEE. In 3 cases, TEE clearly demonstrated an intracardiac extension of the mass, not detected by CT (Figure 2). In 30 cases, in which CT was not diagnostic, TEE allowed us to diagnose or exclude the infiltration of cardiovascular structures. In 1 case, a mass considered to be vascular by CT was identified as solid by TEE (this was confirmed by surgery). Four of the patients for whom TEE gave anatomic data
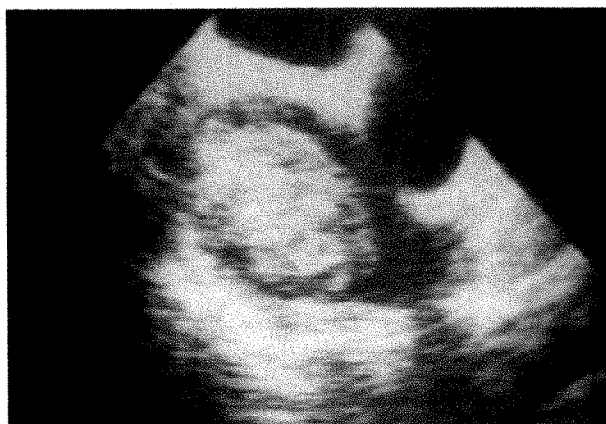
FIGURE 3. This 56-year-old man was first admitted in a different hospital, where an unresectable lung cancer infiltrating the right atrium had been diagnosed by computed tomography. He was sent for oncologic evaluation to our hospital, and underwent transesophageal echocardiography within the prospective study. Transesophageal echocardiography showed a 5 × 4 cm intracardiac mass limited to the right atrium, without any extracardiac extension. Surgery was then suggested: a benign angiotelioma was resected.

different from those from the CT underwent open-chest surgery: TEE data were confirmed in every patient (Figure 3). In 1 patient, in whom TEE detected a residual mass after chemotherapy and CT did not, the clinical outcome confirmed the TEE diagnosis. In 34 patients, TEE gave additional hemodynamic data not obtained by any other imaging technique.

The main fields in which TEE was superior to radiologic techniques and transthoracic echocardiography were: (1) assessment of pericardial infiltration; (2) differential diagnosis between vascular and nonvascular lesions (Figure 1); (3) study of superior vena cava and pulmonary vein flow (Figure 4); (4) assessment of the infiltration of the descending thoracic aorta; and (5) study of the pulmonary artery and its branches (Figure 5). However, the qualitative ultrasonic tissue characterization did not allow us to differentiate neoplasm from fibrosis in patients treated by chemotherapy or radiation therapy in every case. In fact, in 3 patients the residual mass was supposed to be fibrotic because it showed an homogeneous, high-intensity echogenicity; on the contrary, within the mass (partially fibrotic) some

FIGURE 4. This 35-year-old woman with highly malignant non-Hodgkin's lymphoma localized in the upper and middle mediastinum was studied prospectively. Transthoracic echocardiography showed a large mass with parenchimal-like echogenicity, compressing the cephalic portion of the superior vena cava (A). Color and pulsed Doppler confirmed the presence of a disturbed flow. At transesophageal echocardiography the caudal portion of the superior vena cava appeared of normal shape and diameter. Doppler sampling showed a normal flow (B).

neoplastic tissue was still present. In another patient, a mass without homogeneous echogenicity was found to be probably fibrotic with nuclear magnetic resonance.

DISCUSSION

The presence, site and size of mediastinal neoplasms is usually assessed by CT. Two-dimensional echocardiography, combined with radiologic techniques, is useful in obtaining additional data that may be helpful in the management of the neoplastic patient, and TEE has been recently introduced in this field.[25] Each technique has advantages and disadvantages. CT can be easily standardized and allows visualization of the whole chest, but it is less precise in defining highly mobile structures, does not give real-time images, and structures are shown on a smaller scale. Moreover, it is more expensive (often not available in small hospitals) and difficult to perform in patients with orthopnea. Transthoracic echocardiography is easy to perform, has a low cost and is available even in small hospitals, but its use is limited mostly to neoplasms of the anterior mediastinum. In our experience, important anatomic information was missed in 67% of examinations. TEE allows a better visualization of the mediastinal structures, with high resolution images, and is easily available; it is slightly more time-consuming and expensive than conventional echocardiography, and still has an imaging field limited to the mediastinum, with "blind areas" due to the airways.

To date, TEE has generally been used in selected cases to solve particular clinical problems. In this study, TEE was performed in 20 patients for the purpose of obtaining additional data. And the new data were relevant in the clinical management of 14 of 20 patients (70%). Furthermore, we studied prospectively 50 patients with mediastinal neoplasms already diagnosed by radiologic techniques and performed 31 follow-up studies. In 34 of these patients (68%) the examination gave additional hemodynamic information that pertained to the flow within the thoracic vessels. This information may have clinical relevance for several reasons. Throm-

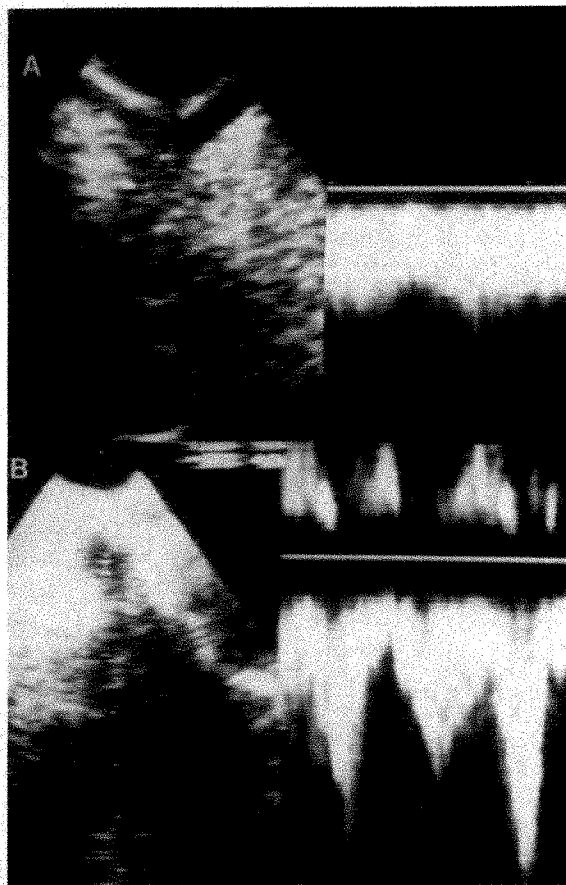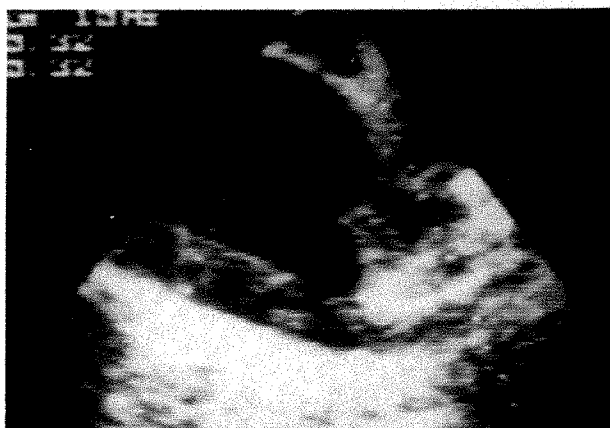

FIGURE 5. This 69-year-old woman affected by non-Hodgkin's lymphoma with a huge mediastinal mass was prospectively examined. Transesophageal echocardiography allowed recognition of the compression of the left pulmonary artery at its bifurcation.

bosis is a well-known complication in the case of compression of the superior vena cava; the detection of compression or infiltration of the vessel by a neoplastic mass may suggest the use of prophylactic anticoagulants even when a superior vena cava syndrome is not clearly evident. The hemodynamic derangement due to the obstruction of the pulmonary artery or pulmonary veins can affect chemotherapy and clinical outcome. In 31 patients, TEE gave anatomic data not obtained by CT, mostly pertaining the infiltration of cardiovascular structures. This allowed for more complete individual planning of antineoplastic therapies in 28 of 31 patients. Furthermore, the therapeutic approach was radically changed in 3 of 31 patients. The diagnosis of the presence or absence of infiltration of the cardiovascular structures may have clinical relevance as a prognostic factor in Hodgkin's disease, and when planning the more appropriate antineoplastic treatment (surgery, radiation therapy or chemotherapy) for both lymphomas and solid tumors, especially if the mediastinal mass can be resected (in order to plan the surgical approach and, possibly, the resection and bypass of the infiltrated vessels).[26-30]

From the present experience, echocardiography should then be considered as a useful complementary technique to CT. With regard to technical problems in performing CT, the use of TEE with color Doppler can be also used as a potential alternative imaging technique. In fact, TEE can be performed even on very sick bedridden patients with orthopnea and in a short time.

TEE can be used to study mediastinal neoplastic masses when other routine imaging techniques (conventional radiology, CT) are not feasible or not completely diagnostic. TEE is usually well-tolerated by even very sick neoplastic patients, supplying additional relevant anatomic or functional data, or both, in most cases. In our experience, the additional data obtained were relevant in the diagnostic or therapeutic decision-making process in 14 of 20 patients (70%) who underwent TEE in order to solve specific diagnostic problems. TEE supplied additional data in 90% of the 50 patients prospectively studied (the therapeutic approach was radically changed in 10% of them). Further studies and a longer follow-up are necessary in order to define whether TEE should be used routinely or only in selected cases in this particular pathology.

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Safety of Intravenous High-Dose Dipyridamole Echocardiography

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Clinical data on 10,451 high-dose (up to 0.84 mg/kg over 10 minutes) dipyridamole-echocardiography tests (DET) performed in 9,122 patients were prospectively collected from 33 echocardiographic laboratories, each contributing >100 tests. All patients were studied for documented or suspected coronary artery disease (1,117 early [<18 days] after acute myocardial infarction and 293 had unstable angina). Significant side effects including major adverse reactions and minor but limiting side effects occurred in 113 patients (1.2%). Major adverse reactions occurred in 7 cases (0.07%). In 6 of these cases, adverse reactions were associated with echocardiographically assessed ischemia and included 1 prolonged cardiac asystole (complicated by acute myocardial infarction and coma, with death after 23 days), 1 short-lasting cardiac asystole, 2 myocardial infarctions, 1 pulmonary edema and 1 sustained ventricular tachycardia. In all 6 cases, the cardiologist-echocardiographer performing the study had a limited experience (<100 tests) with DET, and at off-line reading in 5 cases, the obvious echo-positivity preceded the onset of complications by 1 to 5 minutes. The only ischemia-independent major side effect was a short-lasting cardiac asystole that was reversed by aminophylline and atropine. Significant side effects associated with echocardiographically assessed ischemia occurred in 89 additional cases (21 with and 68 without concomitant echocardiographically assessed myocardial ischemia). The most frequent of these side effects was hypotension or bradycardia, or both, which occurred in 40 patients with negative and 6 with positive DET. In all cases, side effects promptly subsided after aminophylline. In 1,857 cases, the high dose was not given for echo-positivity before the eighth minute. In 60 cases, the full high dose was not given despite the echocardiographic negativity for limiting side effect, yielding an overall feasibility of high-dose DET of 99%. Aminophylline was routinely administered also at the end of negative tests. Noticeable side effects occurred in 17 cases. In 13 patients (7 with negative and 6 with positive DET) transient ST-segment elevation occurred 1 to 4 minutes after the onset of aminophylline infusion, accompanied by regional dyssynergy. All 13 patients had variant angina. Thus, high-dose DET is reasonably safe and well-tolerated, even early after acute myocardial infarction and in patients with unstable angina, when selectively used in patients in whom the lower dose did not induce either echocardiographic signs of ischemia or limiting side effects.

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The dipyridamole-echocardiography test (DET) was recently proposed for the diagnosis of coronary artery disease.[1,2] It is an inexpensive, simple, fast and effective tool for diagnosis,[3-8] as well as for prognostic stratification in various patient subsets,[8-11] as similarly reported by several laboratories. However, it is generally believed that only large-scale multicenter trials can supply the necessary information for an unrestricted acceptance of any new diagnostic procedure,[12] otherwise tests that are hazardous or useless, or both, may become accepted, disseminated and installed as standard procedures before inadequacies are recognized.[13] This is particularly true for DET, because dipyridamole doses higher than those usually used for nuclear myocardial perfusion imaging (and generally considered to be reasonably safe)[14] are needed to yield optimal diagnostic accuracy.[2] To fill this information gap, the Echo-Persantine International Cooperative (EPIC) study was designed to provide what we call (in analogy to the sequential phases of testing of a new drug) the "phase IV" information about this test.[13] The rationale of the EPIC study is to produce results directly relevant

to clinical practice, with minimal interference with the usual diagnostic workup of the patient. It was agreed a priori that each center had to contribute ≥100 DET to enter the study, because this level of expertise is regarded as critical for the reliability of stress-echo readings.[15] This study reports the safety record of DET in a large-scale, multicenter, prospective trial involving 33 echocardiographic laboratories using DET (performed according to a standardized protocol) for clinical purposes in daily diagnostic practice.

METHODS

Patient characteristics: The 10,451 tests were performed in 9,122 patients (7,221 men and 1,901 women, age range 24 to 80 years, mean 56) with known or suspected coronary artery disease; 829 patients underwent >1 (up to 4) DET study to assess the effects of antianginal therapy, or coronary angioplasty or artery bypass procedures, or to evaluate the spontaneous progression of disease. There were 293 patients with history of unstable angina that was recently (<2 days) effectively treated (<2 attacks/day) by antianginal therapy; 1,117 were studied early (<18 days) after an acute uncomplicated myocardial infarction. The remaining patients had history of chest pain or myocardial infarction, or both. Left ventricular function was measured by the mean of the wall motion score index derived from an 11-segment model of the left ventricle; each segment was assigned a score ranging from 1 (normal) to 4 (dyskinetic). Resting left ventricular function ranged from completely normal to markedly altered. In particular, 215 patients evaluated after an acute myocardial infarction had a wall motion score index >1.8, indicating a severely depressed global resting function. Because of time and resource constraints, minor side effects were not taken into consideration: unless otherwise mentioned, these effects were either absent or (when present) well-tolerated, of mild severity or promptly reversed by aminophylline.

Dipyridamole-echocardiography test: Patients were instructed to fast for ≥3 hours before the test and specifically to avoid tea, coffee and cola drinks (the xanthine contents of which can limit dipyridamole action)

for the preceding 12 hours. Two-dimensional echocardiographic and 9- or 12-lead electrocardiographic monitoring were performed in combination with a dipyridamole infusion of 0.56 mg/kg over 4 minutes, followed by 4 minutes of no dose and then 0.28 mg/kg over 2 minutes.[2] The cumulative dose was therefore 0.84 mg/kg over 10 minutes. Aminophylline (240 mg), which promptly reverses the effects of dipyridamole, was available. During the procedure, 1 electrocardiographic lead was continuously displayed on the echo monitor, and the electrocardiogram was recorded each minute. Blood pressure was usually recorded every 1 to 4 minutes by cuff sphygmomanometer. Two-dimensional echocardiograms were continuously obtained and intermittently recorded during and up to 5 to 10 minutes after dipyridamole administration.[3] Also, in case of test negativity, aminophylline (40 to 70 mg over 1 minute) was usually administered at the 15th or 17th minute.[3] Recordings were usually obtained either continuously or intermittently at baseline, after the first dose, before and after the second dose, and before and after aminophylline injection. Commercially available imaging systems were used. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the test, new areas of abnormal wall motion were identified in multiple views when possible. All views (parasternal, apical and subcostal) were obtained when possible, depending on the patient's acoustic window. The apical approach (4- and 2-chamber views) was most frequently used. Echocardiographic images were evaluated on-line by the cardiologist-echocardiographer performing the test. When necessary, videotape recordings were reviewed for analysis.

End points of the test were obvious worsening or de novo occurrence of regional transient dyssynergy, severe chest pain or ST-segment shift >0.2 mV from baseline, and intolerable side effects.

RESULTS

Four categories of side effects were identified as follows: major side effects consisting of life-threatening complications needing specific treatment, ischemia-re-

FIGURE 1. Prevalence of significant (including major) side effects in patients with positivity during dipyridamole-echocardiography test (DET). On *horizontal axis,* minutes from onset of testing are shown (time 0 = beginning of dipyridamole infusion). LV = left ventricular; tachyarr = tachyarrhythmias.
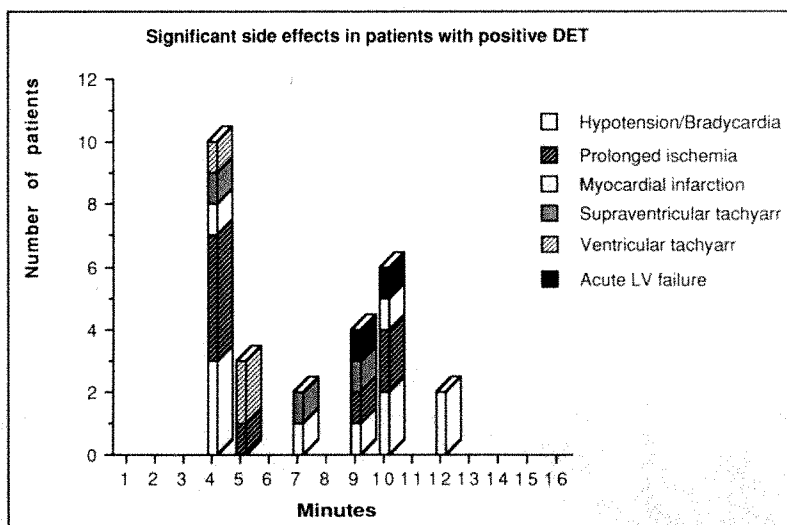
Pt. No.	Age (yr) & Sex	History	Previous DET	Therapy	Timing Complication (min)	WMSI Rest	WMSI Peak Dipyridamole	Complication	Coronary Anatomy	Operator Experience
1	63M	Old MI, angina, previous PTCA	Yes	β blockers, nitrates, nifedipine	10	1.18	1.54	Asystole, MI	LAD 75%	<50
2	65M	Recent MI	No	No	4	1.27	1.45	MI	LAD 100%, LCX 100%	<80
3	73M	Angina, paroxysmal AF	No	Quinidine retard	5	1.18	1.36	V tach	LCX 100%	<50
4	62M	Recent MI	No	No	10	2.36	2.54	Pulmonary edema	LAD 50%, LCX 50%, RCA 99%	<50
5	59M	Unstable angina	No	No	10	1	1.36	MI	Not available	<50
6	51M	Stable angina	No	No	7	1	1.54	Asystole	LM 75%, LAD 90%, LCX 90%	<50
7	53M	Recent MI	No	β blockers, aspirin	3	1.36	1.36	Asystole	Not available	<50

AF = atrial fibrillation; DET = dipyridamole-echocardiography test; LAD = left anterior descending; LCX = left circumflex; LM = left main; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; V tach = ventricular tachycardia; WMSI = wall motion score index.

lated side effects associated with and following echocardiographic positivity, ischemia-independent side effects that occurred in the absence of echocardiographically detectable ischemia, and aminophylline-related reactions appearing after the onset of the antidotal infusion. The temporal distribution of ischemia-related side effects (including major complications) during the test is displayed in Figure 1; it tends to mirror the bimodal temporal distribution of echocardiographic positivity during the test, with a higher peak at the end of the first dose and a second peak at the end of the second dose. The temporal distribution of ischemia-independent side effects is displayed in Figure 2; a more marked, earlier peak can be observed soon after the first dose, with tendentiously unimodal distribution and a rightward skewness. Significant side effects including major adverse reactions and minor but limiting side effects occurred in 113 patients (1.2%).

Major adverse reactions: Of 10,451 DETs in this study, 7 (0.07%) were accompanied by major adverse events. The only ischemia-independent major side effect was a short-lasting cardiac asystole that was reversed by aminophylline and atropine. In this patient a subsequent electrophysiologic study documented a severe sick sinus syndrome. In the remaining 6 cases, adverse events were associated with echocardiographically detected ischemia

(Table I). There was 1 sustained ventricular tachycardia (in a patient with history of atrial fibrillation who was receiving quinidine therapy) lasting 2 minutes and abolished by aminophylline; 1 florid pulmonary edema needing intubation and mechanical ventilation; 2 patients with myocardial ischemia (with persisting dyssynergy, chest pain and ST-segment changes) resistant to aminophylline, nitrates and β blockers, which progressed to small uneventful myocardial infarction; 1 cardiac asystole associated with anterior ischemia, lasting <10 seconds and promptly reversed by aminophylline and atropine; and 1 prolonged cardiac asystole resistant to aminophylline and associated with infarction, coma and death after 23 days. In the latter case, a transient septoapical ischemia (accompanied by pseudonormalization of a basally negative T wave in V_2) was followed by a severe bradycardic reaction that progressed to cardiac asystole. Cardiac asystole was resistant to aminophylline and lasted 35 minutes before a normal frequency was restored by ventricular pacing. The patient developed an acute transmural myocardial infarction, followed by grade III coma with ventilatory mechanical assistance and parenteral nutrition. He died after 23 days with the diagnosis of sepsis and systemic compromise. The patient underwent a DET 3 months before; the test had been positive for ischemia in exactly
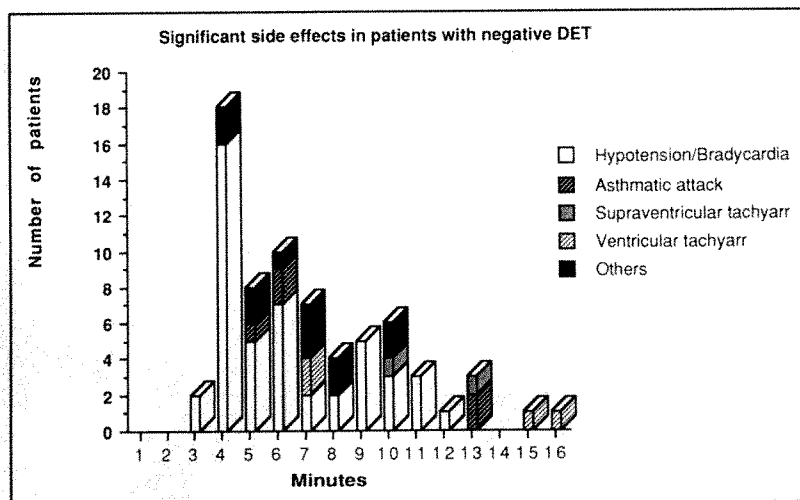

FIGURE 2. Prevalence of significant (including major) side effects in patients with negativity during dipyridamole-echocardiography test (DET). On _horizontal axis_, minutes from onset of testing are shown (time 0 = beginning of dipyridamole infusion). tachyarr = tachyarrhythmias.

the same region (septoapical), and the dyssynergy appeared at the 6th minute (so that the high dose was not administered). After the first DET, the patient underwent coronary angiography (showing 90% stenosis of the left anterior descending coronary artery), and coronary angioplasty was subsequently performed. The procedure was unsuccessful, and the patient underwent the second DET while receiving full antianginal therapy (nitrates, nifedipine and β blockers). There were 2 differences between the first uneventful and second complicated DET: the dose administered (lower in the first and one higher dose in the second) and the concomitant antianginal therapy (off treatment at the first test, and receiving full therapy at the second).

Significant side effects associated with ischemia: Significant side effects occurred in 21 additional cases with echocardiographically documented ischemia. One patient developed acute left ventricular failure with intense dyspnea, which was promptly resolved by aminophylline and diuretics. Two patients had supraventricular tachycardia (needing intravenous verapamil). One patient had an atrial fibrillation with secondary hypotension (blood pressure decrease >30 mm Hg), and 2 had unsustained ventricular tachycardia (5 and 4 beats, respectively). In 6 patients, myocardial ischemia was accompanied by a hypotensive or bradycardic reaction, or both. One patient had atrioventricular dissociation. In 8 patients, ischemia was resistant to aminophylline and nitrates; β blockers (n = 7) or verapamil (n = 1) were needed, and peripheral thrombolytic therapy was used in 1.

Of 68 patients with significant ischemia-independent adverse reactions, symptomatic hypotension occurred in 22, symptomatic hypotension and bradycardia in 18, and second degree 2:1 atrioventricular block in 5. In some cases, the cardioinhibitory reaction was accompanied by variable degrees of autonomic overactivity, evidenced by pallor, sweating and nausea. All these events were promptly reversed by aminophylline; atropine was also administered to 5 patients. Dyspnea with bronchospasm occurred in 5 patients. Four patients had ventricular tachyarrhythmias (triplets and couplets at the 7th

minute in 2, one run of 5 beats at the 15th minute, and 1 accelerated idioventricular rhythm lasting 1 minute and spontaneously reverting to sinus rhythm at the 16th minute). There was 1 atrial fibrillation and 1 paroxysm of supraventricular tachycardia. In 11 additional cases, the high dose could not be administered owing to headache (n = 2), vomiting (n = 3), nausea (n = 2) and palpitations with tachycardia >130 beats/min (n = 4). One patient fell asleep during the test in the absence of myocardial ischemia or neurologic signs and with stability of hemodynamic parameters (blood pressure and heart rate). Consciousness was immediately restored by aminophylline infusion.

Of all significant side effects unrelated to ischemia, 49 episodes occurred within the first 8 minutes, and 11 between the 9th and 10th minute. In 60 cases, the full high dose was not administered despite the echocardiographic negativity for limiting side effect, yielding an overall feasibility of high-dose DET of 99%. In 1,857 cases, the high dose was not administered for echo-positivity occurring before the 8th minute.

Aminophylline was routinely administered to all patients also at the end of negative tests. Significant side effects occurred in 17 cases (Figure 3). In 13 patients (7 with negative and 6 with positive DET) transient ST-segment elevation occurred 1 to 4 minutes after the onset of the aminophylline infusion, always accompanied by regional dyssynergy (with chest pain in 11 cases), and was promptly relieved by sublingual nitrates. All these patients had variant angina; in 5, the diagnosis was unknown up to the time of testing and was subsequently confirmed by ergonovine test. In 1 patient, an atrial fibrillation episode occurred 30 seconds after the onset of aminophylline administration. In 3 cases, a short-lasting hypotension/bradycardia reaction occurred a few seconds after the onset of aminophylline infusion.

Identification of patients prone to major adverse reactions: Table I lists the main clinical features of patients with major complications during the test. Age, clinical conditions (unstable angina or recent myocardial infarction) or resting left ventricular function were

FIGURE 3. Prevalence of side effects after onset of aminophylline injection. On *horizontal axis*, minutes after beginning of aminophylline injection.
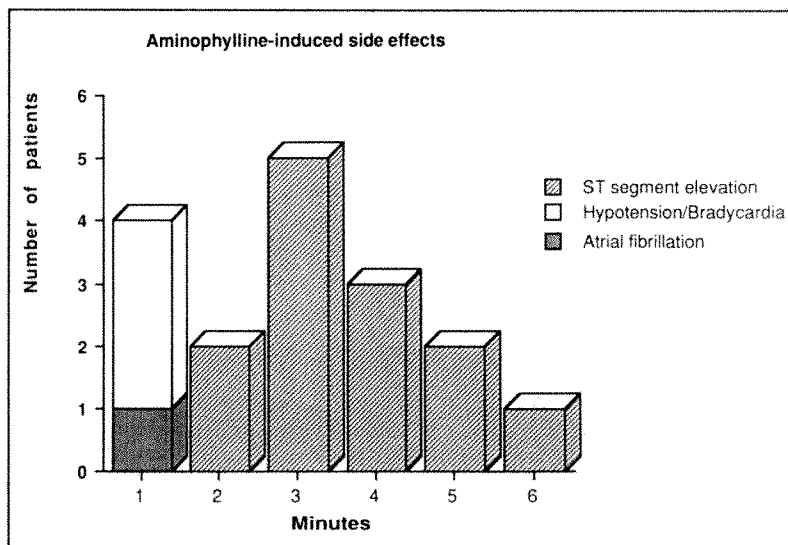
not found to be discriminant. Two of 3 patients with cardiac asystole were receiving β blockers at the time of testing. In 3 of 7 complicated studies, the adverse reaction appeared immediately after high-dose administration. The only critical factor appeared to be the expertise of the cardiologist-echocardiographer performing the study. Major side effects were more frequent in studies performed by an operator still in the learning curve (i.e., <100 stress-echo studies performed). In 5 of 6 cases with ischemia-related adverse reactions, the blind reading of tapes by an experienced observer evidenced an obvious transient dyssynergy well before (2 to 5 minutes) onset of the complication. In all 3 cases with high-dose complications, the experienced observer would have considered the test positive before the 8th minute, thus avoiding the high-dose administration that actually caused the adverse reaction.

Side effects and diagnostic serendipity: Although unwanted, side effects may offer useful diagnostic clues. Aminophylline-induced ST-segment elevation was a very specific sign of variant angina, whose diagnosis was elusive up to the time of testing in 5 patients. Three patients who developed an asthmatic attack had been referred to testing for chest discomfort, which was reproduced by dipyridamole infusion. The diagnosis of asthma was further confirmed by pulmonary function tests. In 1 patient, ischemia-independent ventricular asystole revealed severe sick sinus syndrome that was later documented by electrophysiologic study.

DISCUSSION

This study establishes the safety of high-dose DET in the largest population of patients available to date.

The availability of a highly reliable, "real-time" echocardiographic marker of myocardial ischemia allows 2 large categories of significant side effects to be identified: those related to ischemia (i.e., associated with and following obvious echo-positivity) and those occurring despite echocardiographic negativity. The most frequent unwanted effect was a cardioinhibitory reaction.

Cardioinhibitory reaction: Isolated arterial hypotension may be due to an individual hypersensitivity to the systemic arteriolar dilatory effects of adenosine. The inhibitory "vagal-like" reaction (consisting of dizziness, hypotension or bradycardia or a combination) may represent a reflex triggered by ischemia, but it occurred more frequently in the absence of ischemia. The dipyridamole-induced cardioinhibitory reaction has 2 possible ischemia-independent substrates, 1 electrophysiologic and 1 neurophysiologic.

Dipyridamole acts through accumulation of endogenous adenosine[16] and has much less prominent electrophysiologic effects than does exogenously administered adenosine.[17] However, intravenous dipyridamole acts as a depressor of sinus and atrioventricular nodal function[17]; accordingly, severe bradycardia may be the presenting symptom of an occult severe sick sinus syndrome,[18,19] because it was actually documented by an electrophysiologic study in the patient with ischemia-independent ventricular asystole. A second mechanism involves a neurally mediated sympathoinhibitory reflex,

determining hypotension (through sympathetic inhibition and parasympathetic activation) and vasodilation (through inhibition of sympathetic vasoconstrictor noradrenergic nerves) in humans.[20] This mechanism is consistent with the frequent finding that a cardioinhibitory reaction is accompanied and preceded by signs of autonomic overactivity. The mechanisms that mediate these episodes are still unclear, but probably involve the cardiac mechanoreflex.[20]

Comparison with previous studies: Our data can be considered consistent with scattered, anecdotal reports of serious unwanted side effects during dipyridamole infusion, including death,[21] cardiac arrest,[22] ventricular dysrhythmias,[23] acute pulmonary edema,[24] prolonged ischemia with coronary occlusion,[25,26] acute myocardial infarction[27] and symptomatic bradycardia.[18] It has also been reported that aminophylline termination of the test can result in either hypotension-bradycardia reaction[28] or coronary vasospasm in susceptible patients.[29] However, only large-scale studies can establish the actual prevalence of unwanted side effects due to dipyridamole stress. The results of this study compare favorably with the safety record of dipyridamole-thallium scintigraphy,[14] despite the lower dipyridamole dose used for nuclear perfusion imaging and the wider spectrum of the disease tested in the present study. Ranhosky and Kempthorne-Rawson[14] reported 2 deaths and 2 nonfatal myocardial infarctions in 3,911 patients tested with standard low-dose dipyridamole. The apparent paradox of the higher dose having a higher safety record can be easily explained by considering the echo-test protocol, which includes continuous echo monitoring from the beginning of the infusion and the occurrence of obvious transient dyssynergy as an absolute end point of the test needing prompt aminophylline administration. The safety record of high-dose DET also appears comparable to that of exercise-electrocardiography testing. Although exercise testing is considered a safe procedure, there are reports of acute infarctions and deaths. Multiple surveys confirm that up to 10 myocardial infarctions or deaths, or both, can be expected per 10,000 tests.[30] However, this rate of complications has been achieved after almost 50 years of experience with the test, leading to a progressive refinement of indications and contraindications, standardized treatment of complications, and specific criteria for the instrumentation and expertise needed.

Clinical implications: We believe the safety of the test protocol used is enhanced by the availability of an imaging technique such as 2-dimensional echocardiography providing real-time, beat-to-beat monitoring of regional left ventricular function. Myocardial ischemia resistant to aminophylline can occur and should be treated with sublingual or intravenous nitrates, or both. Nitrate-resistant ischemia occurs infrequently and is usually responsive to intravenous β-blockers. If ischemia is still persistent after aminophylline, nitrates and β blockers, peripheral thrombolysis is advisable to terminate the infarction.

Severe bradycardia (associated with or independent of myocardial ischemia) up to ventricular asystole may

also occur, representing the extreme and life-threatening end of a spectrum whose opposite end is the much more frequent and benign "vagal" hypotension-bradycardia reaction. It should be treated in a stepped-care fashion by putting the patient in the Trendelemburg position and injecting aminophylline and (if necessary) atropine. Aminophylline should be available for injection before beginning the test. In the echo laboratory, there should be the expertise and the facilities of resuscitation procedures.

Because all major complications occurred with unexperienced stress echocardiographers, and in 3 cases during or immediately after high-dose administration, it is advisable that the absolute beginner in stress echocardiography begin his/her own learning curve with the lower (0.56 mg/kg over 4 minutes) dose, progressing to the standard high-dose protocol after completion of training (need ≤100 studies).[15] The pretest clinical features of patients were not helpful in identifying those susceptible to severe adverse reactions.

If these simple precautions, contraindications and standardized treatments of serious unwanted side effects are considered, the safety record of DET may become even better. The feasibility and safety data further confirm the potential role of DET as a fast, inexpensive and efficient diagnostic option in patients with known or suspected coronary artery disease. The next 10,000 studies should take advantage of the experience gathered in these first 10,000, keeping in mind that "what we call experience is often a dreadful list of ghastly mistakes" (J. Chambers Da Costa, MD, 1863–1933).

APPENDIX

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Left Ventricular Mass Quantitation Using Single-Phase Cardiac Magnetic Resonance Imaging

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Magnetic resonance imaging (MRI) has been used to measure left ventricular (LV) mass in animals with superior accuracy. However, its use in cardiac patients has been limited by the long total scan times necessitated by imaging the heart at end-diastole at each of 8 to 10 slice locations. Recent canine studies showed that LV mass may be determined accurately, with considerable timesavings, by use of sequential images throughout the cardiac cycle (single-phase MRI). Twenty normal subjects underwent spin-echo MRI to determine the relationship between LV mass computed from single-phase MRI and results obtained from the more time-consuming end-diastolic MRI (which was used as the reference standard for this study). The left ventricle was spanned with 2 interleaved series of 5 short-axis 1 cm thick slices. 5 images, evenly spaced throughout the cardiac cycle, were obtained at each slice location in all subjects. LV mass ranged from 86 to 198 g. Although end-diastolic LV mass exceeded single-phase results by an average of 5 g (p <0.002), there was a close correlation between the 2 (slope = 0.99; r = 0.96). Although LV mass derived from end-diastolic images exceeded single-phase results, this difference is unlikely to be clinically significant and is small compared with the standard error of echocardiographic methods. Furthermore, when the order in which single-phase images were selected was reversed, there was improved agreement with end-diastolic MRI. Thus, the close correlation between single-phase and end-diastolic results indicates that single-phase MRI may be a practical, time-efficient method to determine LV mass in humans with normal LV shape.
(Am J Cardiol 1992;70:259–262).

Recent studies documented the ability of magnetic resonance imaging (MRI) to quantitate left ventricular (LV) mass with superior accuracy in both excised hearts[1] and experimental animals in vivo.[2-4] Previously reported spin-echo MRI LV mass calculations were obtained using Simpson's rule reconstruction of end-diastolic images obtained at each slice location.[4,5] However, the total scan time needed to obtain end-diastolic spin-echo images at each of 8 to 10 slice locations in subjects with slow heart rates may range from 45 to 60 minutes and therefore make MRI determination of LV mass impractical for many cardiac patients. Recent in vivo canine studies showed that LV mass may be determined accurately when images from different phases of the cardiac cycle are used,[6] calling into question the necessity of imaging each slice location at end-diastole. The use of a multislice, single-phase MRI protocol (with an image at each sequential slice location obtained at a different phase of the cardiac cycle) may therefore permit accurate LV mass determination in cardiac patients with dramatically shortened total MRI time. Therefore, single-phase MRI would potentially be a practical strategy for determining LV mass. Twenty normal subjects underwent multiphase, multislice MRI to determine the relationship between LV mass computed from single-phase MRI and results obtained when end-diastolic images are used. We then compared LV mass determinations (using Simpson's rule) obtained from end-diastolic images with those of a simulated single-phase MRI protocol obtained by selecting sequential images from the multiphase, multislice matrix.

METHODS

Magnetic resonance imaging technique: Twenty normal subjects underwent gated cardiac MRI using spin-echo technique on a 1.5 Telsa Signa system (General Electric, Milwaukee, Wisconsin). Echo time was 20 ms, and repetition time was equal to the RR interval; the image matrix was 128 × 256, and field of view was 24, 32 or 40 cm, depending on subject's size. An ungated coronal localizing series established the thoracic landmarks in each case. MRI along the true cardiac short axis was performed by double oblique angulation using the method described by Clark et al[7] (Figure 1).

The entire LV volume was encompassed with 2 sets of 5 interleaved 1 cm thick slices with a 1 cm interslice distance using multiphase/multislice MRI. Thus, after 2 acquisitions the entire left ventricle was imaged in contiguous 1 cm thick slices. Usually, 8 to 10 slices (mean 9.2) were needed to image the left ventricle. Im-

ages were obtained at evenly spaced intervals throughout the cardiac cycle (Figure 2). Five images were obtained at each slice location for a total of 50 images in each subject. The end-diastolic image at each slice location was obtained at 4 ms from the R wave. Total MRI time comprised approximately 5 minutes for the coronal series and from 16 to 25 minutes for each short-axis series, using 2 excitations for each acquisition. Thus, total scan time for subjects in this series varied from approximately 40 to 55 minutes.

Planimetry: Images were interactively analyzed by planimetry from film hard copy by an experienced operator using a commercially available personal computer-based program. For each study, window and contrast levels were set at the time of scanning to optimize the myocardial/cavity interface. A video camera displayed images from the backlit hard copy on a television screen for planimetry. For each image demonstrating myocardium, the cavity area and myocardial area were obtained in triplicate by planimetry using a mouse. Mus-

cle volume for each slice was the product of myocardial area and slice thickness. Likewise, cavity volume was the product of cavity area and slice thickness. Myocardial and cavity volume were computed by Simpson's rule reconstruction: $V = \Sigma A_i T$, where V = total volume (cavity or myocardial); A = area by planimetry; T = slice thickness; and i = slice number. Myocardial volume was multiplied by specific gravity (assumed to be 1.05 g/ml) to estimate myocardial mass.

Correlation with cardiac phase (Figures 2 and 3): For each subject, LV mass was computed by Simpson's rule reconstruction from both end-diastolic and single-phase images (Figure 2). For this method, the image was chosen at each slice location to simulate a single-phase MRI protocol and thus corresponded to the shortest trigger delay for the first slice location, the next longest delay for the second location and the longest delay for the fifth slice. The sequence was repeated for each image displaying myocardium in the second acquisition. Single-phase LV mass was calculated twice. First, the images were chosen with the most apical slice at the shortest trigger delay (Figure 2). The entire procedure was repeated with images selected in the reverse order (reverse phase) with the shortest trigger delay image beginning with the most basal slice location, which showed myocardium, and proceeding sequentially.

Statistics: LV mass from single- and reverse-phase image reconstruction methods was compared with results of end-diastolic images by linear regression. Mean values for LV mass obtained by various methods were compared by analysis of variance for repeated measures, with $p < 0.05$ considered statistically significant.

RESULTS

LV mass ranged from 86 to 198 g (Table I). Diastolic exceeded single-phase LV mass by an average of 5 g (125 vs 121; $p < 0.002$) when the shortest trigger delay image was at the most apical slice location ("apex to base"; Figure 4). Diastolic and single-phase LV mass correlated closely ($r = 0.96$; slope = 0.99; SEE 9 g over the range of values 86 to 198 g). However, when images were chosen with the most basal image at the shortest trigger delay ("reverse phase"; Figure 5), there was
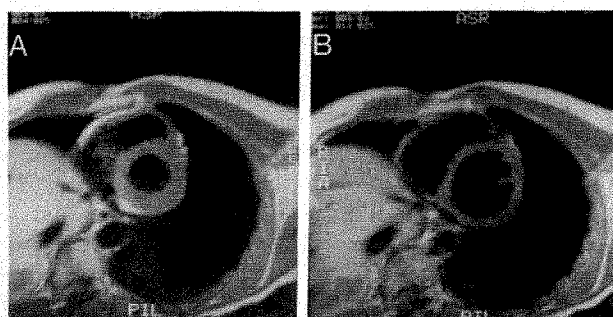

FIGURE 1. Representative end-diastolic image obtained using double-oblique angulation. A, systolic image (trigger delay of 281 ms from R wave), and B, end-diastolic image (trigger delay of 4 ms). There is excellent cavity definition due to uniform signal void from blood pool and intermediate signal from myocardium.

IMAGE SELECTION: APEX TO BASE

TRIGGER DELAY (ms)

SLICE					
1	4	139	274	409	544
2	4	139	274	409	544
3	4	139	274	409	544
4	4	139	274	409	544
5	4	139	274	409	544

diastolic   phase

FIGURE 2. Images selected in 1 acquisition for both end-diastolic (second column) and simulated single-phase images. Each complete study comprised 10 slice locations. Trigger delay is number of ms from R wave. End-diastolic image was chosen as 4 ms image at each slice location; single-phase image was chosen sequentially (diagonally oriented boxes from top to bottom). Thus, 4 ms image was obtained at apex. Image selection process was performed in similar manner for second acquisition.

IMAGE SELECTION: BASE TO APEX

TRIGGER DELAY (ms)

SLICE					
1	4	139	274	409	544
2	4	139	274	409	544
3	4	139	274	409	544
4	4	139	274	409	544
5	4	139	274	409	544

FIGURE 3. Images selected in base-to-apex ("reverse phase") direction. At most apical slice location, 544 ms image was chosen; at 10 mm farther along long axis of left ventricle, 409 ms image was chosen.

closer agreement (125 g for end-diastolic and 126 g for reverse phase; p = not significant) with an equally close correlation (r = 0.97; slope = 0.94; SEE 8 g over the range of values 91 to 198 g).

DISCUSSION

LV hypertrophy has been shown to be an independent predictor of cardiovascular morbidity and mortality.[8-11] Furthermore, recent echocardiographic studies established that the risk of cardiovascular morbidity and mortality varies, with LV mass as a continuous variable.[8,10] However, echocardiographic determination of LV mass has important limitations; in ideal circumstances, the standard error of the technique is ≥ 30 g,[12] rendering it insensitive to small changes in LV mass produced by clinical intervention. Moreover, M-mode echocardiographic methods necessitate geometric assumptions concerning LV shape, which limit its use in normally shaped ventricles. Finally, the technical quality of this study may be inadequate for LV mass determination in $\geq 20\%$ of subjects.[9]

MRI is an attractive method for LV volume and mass quantitation, because the entire LV volume may be encompassed tomographically, permitting use of Simpson's rule reconstruction. Because MRI techniques provide images with excellent contrast between myocardium and the blood-filled cavity, operator planimetry is feasible,[2,13] and computerized volumetric quantitation may be possible in the future.[1] The validation studies have shown an excellent correlation between MRI LV mass and anatomic weight, in both the normal[2,3,14] and abnormal[6] left ventricle.

However, the use of spin-echo MRI for LV mass determination in humans has been limited by the long total scan times, because LV mass determinations have

TABLE I Left Ventricular Mass (g)				
Age (yr) & Sex	BSA	Single-Phase	Reverse-Phase	End-Diastolic
35F	1.5	86	91	91
32F	1.6	95	99	95
24M	1.6	112	123	110
29M	2.0	153	148	134
38M	1.7	101	99	110
25M	1.9	139	136	145
32M	2.1	139	142	144
37M	1.8	92	103	101
26M	1.9	121	124	127
33F	1.7	98	100	104
28M	1.9	114	117	114
29M	2.0	122	132	127
33M	2.0	129	131	126
29M	1.6	91	103	103
29F	1.6	98	106	109
28M	1.9	126	142	145
29F	1.7	101	103	100
30M	2.0	131	156	151
31M	2.0	176	172	173
27M	2.0	192	190	198
Mean		121	126*	125

*p < 0.002
Left ventricular mass for 20 normal subjects grouped according to method of image reconstruction. Group means are shown.
BSA = body surface area.

usually been obtained from end-diastolic images obtained at each slice location.[4,5,15] Acquisition of end-diastolic images at each of 8 slice locations using the multiphase/multislice approach we outlined requires ≥ 45 minutes of total imaging time, assuming 2 signal averages and an average heart rate of 70 beats/min. Therefore, strategies aimed at reducing total scan time without sacrificing volumetric accuracy would be desirable.
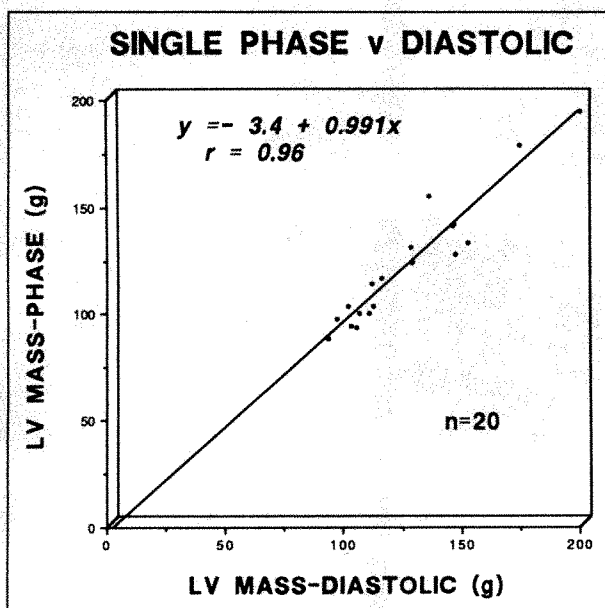
FIGURE 4. Regression showing correlation between left ventricular (LV) mass obtained from end-diastolic images (x axis) and results of single-phase imaging (y axis) when images were reconstructed in apex-to-base direction. There was excellent correlation between the 2 methods (r = 0.96; slope = 0.991; SEE 8.7 g over range of values 85.6 to 198 g).
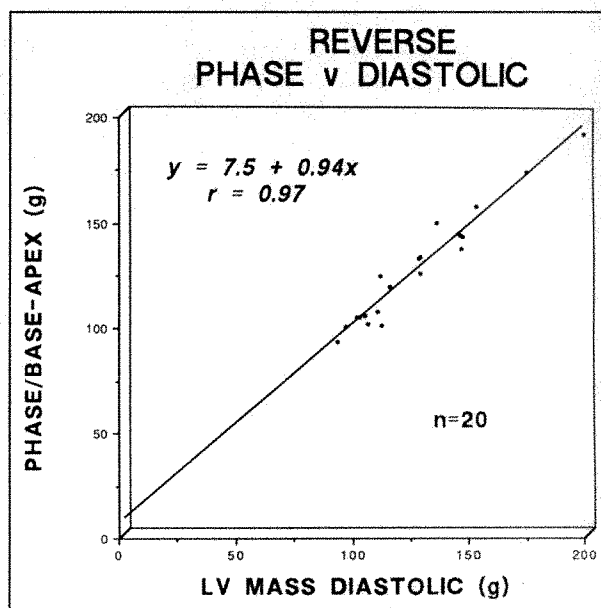

FIGURE 5. Regression showing correlation between end-diastolic left ventricular (LV) mass and single-phase images when reconstructed in base-to-apex "reverse phase" orientation. Reverse phase results also correlated closely with end-diastolic results (r = 0.97; slope = 0.94; SEE 7.6 g over range of values 91.1 to 198 g).

The in vivo canine study of Shapiro et al[6] demonstrated that LV mass may be determined with equivalent accuracy using either end-diastolic (r = .94; SEE 9 g) or end-systolic (r = 0.97; SEE = 7 g) frames. That study also demonstrated that a standard multislice/single-phase algorithm may be used to estimate LV mass with an accuracy equivalent to that of end-diastolic MRI. Therefore, we performed the present study to investigate the correlation between LV mass computed from end-diastolic images and from selected images from the multiphase/multislice matrix that simulated a single-phase protocol.

The results indicate that in normal hearts, LV mass determined from end-diastolic images correlates well with results obtained from the simulated single-phase protocol. The timesavings associated with the use of a single-phase approach is considerable. This timesavings results directly from shortened acquisition times, because setup time (typically 5 to 10 minutes) would be similar for both single-phase and multiphase MRI. For a subject with a heart rate of 75 beats/min, 2 multislice/multiphase acquisitions (with 2 signal averages) comprising 10 slices would need 34 minutes. In contrast, 2 multislice/single-phase acquisitions for the same subject (using 2 signal averages) would require approximately 8 minutes, representing a 26-minute savings in acquisition time; total scan time (including setup) would be approximately 20 minutes.

End-diastolic LV mass slightly (but significantly) exceeded single-phase LV mass when images were chosen in an apex-to-base orientation. This difference is unlikely to be clinically significant and is small compared with the SEE associated with M-mode echocardiography.[12] Furthermore, when LV mass using "reverse-phase" (base-to-apex) reconstruction is compared with end-diastolic images, a smaller discrepancy is observed. The close agreement between end-diastolic and single-phase results may be explained by the considerable time-averaging that occurs for each image when the spin-echo technique is used. Moreover, the images were obtained at evenly spaced intervals throughout the cardiac cycle; with this approach, 3 of 5 images are obtained in diastole. Although it is possible that the greater diastolic myocardial blood content[16,17] may lead to slightly higher diastolic LV mass, it is unlikely that this technique is sensitive enough to detect this difference.

We also observed that when images are reconstructed with the most basal image obtained at end-diastole, the resulting LV mass more closely approximates end-diastolic results than when single-phase images are chosen in the opposite order. Although the explanation for these findings is not completely clear, the likely mechanism may be related to the through-plane motion of the left ventricle. Recent work showed that there is consid-

erable long-axis shortening in the normally functioning left ventricle, which appears to be greatest in basal systolic segments.[6] Such base-to-apex movement may be expected to result in an underestimation of LV mass on short-axis single-phase images, because myocardium at more basal levels of the ventricle would have moved out of the imaging plane on systolic images and been "replaced" by tissue from the mitral annulus, left atrium or aorta. To the extent that the apex-to-base direction of reconstruction included more systolic basal slices, this method would have provided a slightly smaller value for total LV mass than would either end-diastolic or single-phase MRI with a base-to-apex direction of reconstruction.

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Morphologic Findings in Explanted Mitroflow Pericardial Bioprosthetic Valves

Kirsten McGonagle-Wolff, and Frederick J. Schoen, MD, PhD

Intrinsic structural deterioration (primary tissue degeneration) is the leading cause of failure of both Ionescu-Shiley and Hancock pericardial heart valves, as well as porcine aortic valve bioprostheses.[1-4] Although cuspal calcification is clearly the principal contributory pathologic process to failure of porcine valves, the relative roles of calcium, noncalcific tearing and other degenerative processes in pericardial valve failure are less well-established.[4] Early to intermediate clinical results with the Mitroflow® (Mitroflow International, Inc., Richmond, British Columbia, Canada) pericardial heart valve have been favorable.[5,6] The present study sought to identify the morphologic changes and mechanisms of failure after long-term clinical function of this prosthesis.

Sixty-two Mitroflow pericardial heart valves, explanted at surgery or autopsy at many institutions worldwide, were studied, and complications were categorized, as previously described.[4] Clinical data were provided by Symbion Medical of Canada (Richmond, British Columbia). Fifty-five failed valves (24 mitral and 31 aortic) were removed after 0.5 to 84 months (mean 39), and 7 valves were removed incidentally after 0 to 82 months (mean 35) (2 together with a failed valve, and 5 for nonvalve-related complications). At original implantation, patients were aged 9 to 77 years (mean 56) (7 patients aged <35).

Primary causes of valve failure included thrombosis/thromboembolism (2%), endocarditis (11%), nonstructural dysfunction (9%) and structural deterioration (78%) (Table I). In 1 case, death was related to cerebral and renal emboli 8 months after implantation of a valve that had a large, poorly adherent, bland thrombus involving the sinus of Valsalva of 1 cusp, and a centrally located thrombus on the outflow surface of a second cusp. Infective endocarditis was the cause of failure of 6 aortic valves removed at 5 to 40 months (mean 15); none had cuspal tears or perforations, but minimal extrinsic mineralization was present within the vegetations of 3 with active infection. Nonstructural dysfunction included bland paravalvular leak (1 aortic), looped suture (3 mitral) and tissue overgrowth (1 aortic).

Structural deterioration (intrinsic degenerative dysfunction and primary tissue failure) was the cause of failure of 43 valves at a mean of 58 months (range 1.5 to 84) after implantation (Tables I and II). Primary tissue degeneration was characterized by cuspal tears or intrinsic calcification, or both, with or without cuspal thickening, stretching, abrasion, collagen bundle separation, deep fluid insudation, fragmentation of the cuspal inflow surface, inflammatory cell infiltrate and secondary mural thrombotic deposits (Figure 1). Noncalcific cus-

pal tearing was the most frequent mode of failure (21 valves; 49% of those with structural deterioration). Forty-nine cuspal tears involved 35 valves, with or without calcification. Cuspal tears were located adjacent to the commissures with involvement of the free edge, and ranged in size from 1 to 13 mm. Of the 43 valves that failed by structural deterioration, 18 (42%) had calcific deposits demonstrable by specimen radiograph and 25 (58%) were free of mineralization at 33 to 84 (mean 58) and 1.5 to 72 (mean 35) months, respectively. Six mitral and 12 aortic valves failed owing to calcification (13 with associated tears leading to regurgitation, and 5 with stenosis). Of valves with calcific failure, 7 had 1+, 4 had 2+, 6 had 3+, and 1 had 4+ radiographic calcific deposits. Intrinsic mineral accumulation predominated in the commissural cuspal tissue (with lesser amounts at the basal attachments, free edge and cusp body) and was deep within the tissue, with occasional ulceration through the surface. Of the 7 valves from patients <35 years, 3 were removed because of primary tissue failure. One of these valves had a noncalcific tear, 1 was stenotic with 2+ calcification, and 1 had a tear with 3+ calcification.

Four valves removed because of regurgitation had structural deterioration, without intrinsic calcification or cuspal tears, but with collagen bundle separation, deep fluid insudation, inflammatory cell infiltrate, mural thrombotic deposits and fragmentation of the inflow surface. Two of these valves had tissue stretching with cuspal redundancy, which resulted in malalignment, prolapse and creasing of the cuspal tissue. Abrasion

TABLE I Causes of Failure of Mitroflow Pericardial Valves

Causes of Failure	Mitral	Aortic	Total
Thrombosis/thromboembolism	0	1	1 (2%)
Infective endocarditis	0	6	6 (11%)
Nonstructural dysfunction	4	1	5 (9%)
Structural deterioration	20	23	43 (78%)
Total	24	31	55

TABLE II Calcification or Tearing, or Both, as Modes of Structural Deterioration Causing Failure of 43 Mitroflow Pericardial Valves

	Calcific Deposits		
Tears	Yes	No	Total
Yes	2/11 (13)* 30%†	13/8 (21) 49%	15/19 (34) 78%
No	4/1 (5) 12%	1/3 (4) 9%	5/4 (9) 22%
Total	6/12 (18) 42%	14/11 (25) 58%	20/23 (43) 100%

*Mitral/aortic (total).
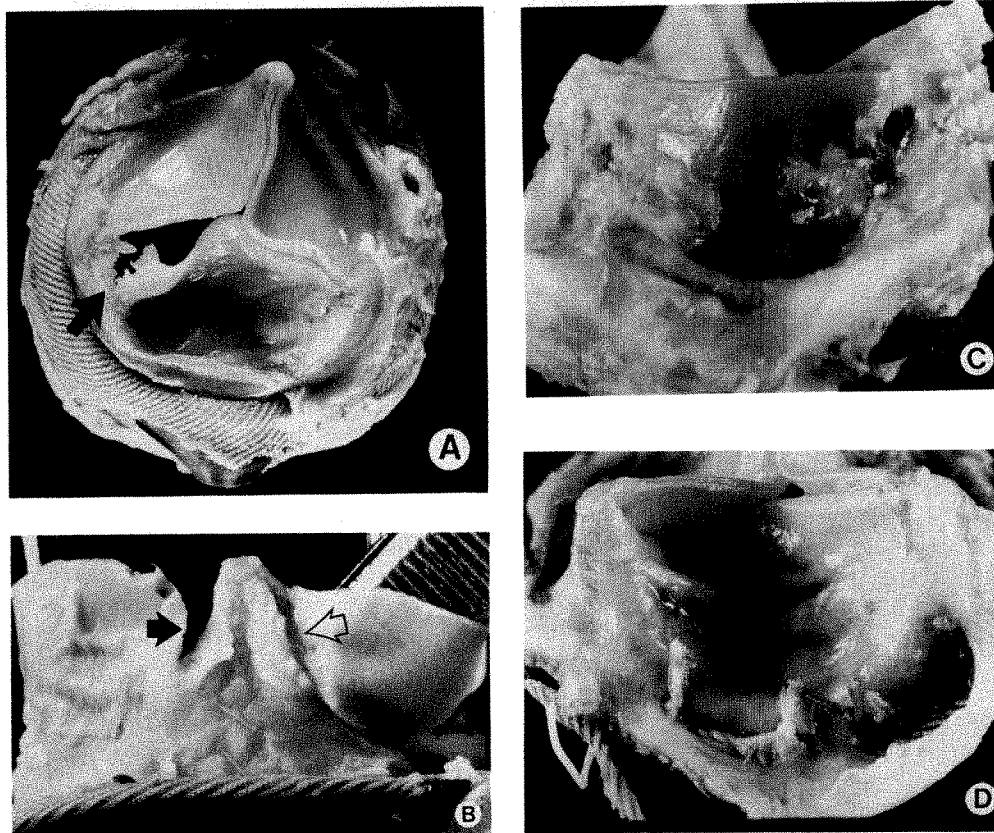†Percentage of total cohort of valves with structural deterioration.

FIGURE 1. Gross morphology of failed valves. *A, inflow view of valve with typical tear adjacent to stent post (arrow). B, cuspal tear (closed arrow) and incipient cuspal tear (open arrow) adjacent to stent post, due to abrasion. C, valve with 3+ calcification and cuspal tear. Calcific deposits ulcerating through cuspal surface (arrow). D, valve without cuspal tear, but with tissue stretching and redundancy, causing regurgitation.*

(*characterized by marked attrition of the outflow collagen bundles and focal cuspal thinning*) *was demonstrated in 3 aortic and 3 mitral valves. Four of these valves had associated cuspal tears. Irrespective of failure mode, nonspecific but frequent microscopic findings included superficially adherent mononuclear inflammatory cells (with occasional deep tissue invasion), rare giant cells, and focal, superficial, small thrombi (23 valves), involving the inflow and outflow surfaces, basal attachment margins and edges of cuspal tears. The 7 valves removed incidentally had minimal pathology; microscopic examination demonstrated orderly architecture of the collagen bundles, and no calcific deposits.*

The major mode of failure of Ionescu-Shiley and Hancock pericardial bioprosthetic valves is cuspal tearing, most frequently without calcification.[1-4] The present study demonstrated structural deterioration as the cause of failure in 79% of Mitroflow pericardial bioprostheses; noncalcific cuspal tears were the cause of 49% of structural failures. Cuspal tears almost exclusively involved the free edge adjacent to the commissures, often in multiple cusps. Underlying cuspal pathology was frequently noted, but whether this was causal or secondary is uncertain. However, calcification was present in and could be contributory to failure in 42% of valves failing through struc-

tural deterioration. In more than two thirds of calcified valves, tears had occurred. Intrinsic cuspal mineralization occurred as early as 33 months in this study and had a morphology similar to that noted in previous studies of pericardial valves.

In summary, primary tissue degeneration is the leading cause of failure of explanted Mitroflow pericardial valves, with the pathologic features largely similar to those reported for other pericardial bioprostheses. Noncalcific cuspal tearing is the dominant pattern; intrinsic calcification (with or without secondary tearing) is an important but less frequent failure mode.

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Electrocardiographic Abnormalities in Mitral Valve Prolapse

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A number of electrocardiographic findings associated with mitral valve prolapse (MVP) have been reported. The most frequent finding is inversion of T waves in the inferior leads,[1-7] which was first described by Humphries and McKusick[7] in patients with late systolic murmurs. The association with MVP was not yet known, and they suggested the term "auscultatory-electrocardiographic syndrome." Other electrocardiographic abnormalities have been reported to consist of ST abnormalities[8] and variable degrees of intraventricular conduction delay, including frank bundle branch block (BBB).[3,4] Jeresaty[4] found a 6% incidence of incomplete right BBB in the absence of atrial septal defects. The incidence of incomplete right BBB was 8% in another study[3]; 3% had associated atrial septal defect. Prolongation of the QT interval in MVP was also noted in several studies.[3,5,8-11] Meyers et al[9] described an increased frequency of QT prolongation in symptomatic patients with MVP compared with in asymptomatic patients, but this difference was not statistically significant. The diagnosis of MVP in many of these studies was primarily obtained by auscultation or based on clinical grounds, or both. Furthermore, in no study that described electrocardiographic findings was a comparison performed with a group of normal subjects. In the present study, we quantify the frequently described electrocardiographic abnormalities in patients in whom the diagnosis of MVP was documented by 2-dimensional echocardiography. These results were compared with those of a control group of patients with completely normal echocardiograms.

Data from all patients in whom invasive and noninvasive cardiologic studies are performed at our institution are entered prospectively into a computerized data base, as described previously.[12] Electrocardiograms were obtained from 148 consecutive patients (men: 32%; and women: 68%; mean age 45 ± 18 years) referred for suspected MVP and with MVP documented by echocardiography. They were analyzed with respect to interventricular conduction disturbances, PR, QRS and QTc intervals, and T-wave abnormalities. The results were compared with electrocardiographic data from 116 patients matched for age and sex (men: 32%; and women:

68%; mean age 47 ± 18 years), but with completely normal echocardiograms. These patients were selected randomly from the echocardiography data base. Discrete data were compared by chi-square analysis. Continuous variables were compared by Student's t test. Power of the test for continuous variables was calculated for mean differences as small as 5% and was >90% in all cases.

The echocardiographic diagnosis of MVP was obtained if there was evidence of ≥1 mm displacement of 1 or both mitral leaflets beyond the plane of the mitral valve annulus during systole in either the parasternal long-axis or apical 4-chamber view.[13] BBB was diagnosed using standard criteria.[14] An incomplete right BBB was diagnosed when the QRS interval was <0.12 ms, and the morphology of the QRS complex was RSR′ in lead V_1 or V_2, or both, together with a prominent S wave in lead I. The values for PR, QRS and QT intervals were obtained by computer analysis. QTc was obtained using the Bazett formula; the upper limit of the QTc interval is 0.39 second for men and 0.44 second for women.[15]

Inversion of the T wave in lead III was found in 57 patients (39%) with MVP and in 20 (17%) without MVP or evidence of heart disease on echocardiography (Table I) (p <0.001). Right bundle branch conduction abnormalities were found in 13 patients (9%) with MVP; right bundle branch involvement occurred in 12 (10%) with normal echocardiograms (p = not significant; Table I). The frequency of QTc prolongation was also not different between groups. A left BBB was found in 1 patient with a normal echocardiogram. Mean values for PR, QRS, QT and QTc intervals for the 2 groups are listed in Table II. There were no significant differences between groups in any of these variables.

In all other previous investigations examining electrocardiographic abnormalities in association with MVP, a comparison was not performed with results obtained from patients matched for age and sex who had no evidence of MVP on echocardiography. In the present study, there was no significant difference in the frequency of a prolonged QTc interval between patients with and without MVP. Furthermore, the mean QTc interval of the 2 groups did not differ significantly. Similarly, there was no significant difference in the incidence of conduction disturbances of the bundle branches. Thus, for most cases of

TABLE I Frequency of Electrocardiographic Abnormalities in Mitral Valve Prolapse

	No. of Pts.	Left BBB	Right BBB Complete	Right BBB Incomplete	QTc Prolongation	T-Wave Inversion
Controls	116	1 (0.8%)	2 (2%)	10 (9%)	23 (20%)	20 (17%)
MVP	148	0 (0%)	4 (3%)	9 (6%)	33 (22%)	57 (39%)*

*p <0.001, chi-square.
BBB = bundle branch block; MVP = mitral valve prolapse.

MVP, the presence of bundle branch conduction abnormalities or QT prolongation is likely unrelated to the presence of MVP and is not important or reliable for diagnostic or prognostic purposes. However, this study did confirm previous studies indicating that repolarization abnormalities (T-wave inversion) in the inferior leads are associated with MVP. The cause of these changes is not known. The possibility that they are caused by abnormalities of regional coronary blood flow with attendant myocardial ischemia has been suggested, although there is little evidence to support this assertion. Potassium depletion and localized myocarditis have also been suggested as possibilities. Repolarization changes in the inferior leads in MVP patients may also be produced by hyperventilation.[8] The significance of this is also unknown.

In summary, our results indicate that MVP is not associated with electrocardiographic abnormalities other than inferior T-wave inversion.

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Does *Enflurane* Effect Ventricular Tachycardia?

A strong prerequisite for surgical ablation of foci of ventricular tachycardia is the ability to induce the dysrhythmia under general anesthesia. Catheter ablation with radio frequency stimulation does not require anesthesia. However, the article by Hief et al.[1] describes an anesthetic technique with little effect on inducibility or rate of ventricular tachycardia. I have 2 concerns with the implied conclusions of the paper. The title of the paper suggests that this is a report on the effects of enflurane on ventricular arrhythmias. However, enflurane was administered in a subanesthetic concentration. One maximal allowable concentration (MAC) is the level of anesthesia at which 50% of patients will not move with painful stimulation. Once an end-tidal concentration of anesthetic is achieved, it must be maintained for several (perhaps 5 to 15) minutes for equilibration with tissue (heart). The duration of stable end-tidal enflurane concentrations before electrophysiologic tests was not stated in the paper. Even if there were adequate time for tissue equilibration, 0.5 to 1 MAC will be subanesthetic in ≥50% of the population. The other adjunctive agent used was nitrous oxide. The relative MAC equivalent would be 0.7 (i.e., nearly equipotent doses of nitrous oxide were used as enflurane). Perhaps combined nitrous oxide and enflurane anesthesia have no effect on ventricular tachycardia. The second concern is with use of thiopental for induction of anesthesia. This agent in dogs has been shown to have prolonged influence on ventricular arrhythmias and electrophysiologic measurements particu-

larly when combined with volatile anesthetics (such as enflurane).[2] The duration of potentiating epinephrine arrhythmias may exceed 4 hours when enflurane is the primary anesthetic. Although rarely used clinically the effects of a "pure" enflurane anesthetic on ischemic ventricular tachycardia have been recently reported.[3] In this study enflurane suppressed the induction of ventricular tachycardia in 60% of the dogs. Enflurane prolonged refractory periods in both the ischemic and normal zones suggesting a class III action. The actions of enflurane were similar to those of halothane, and were in general agreement with the results of Hunt and Ross.[4]

The combined use of short-acting barbiturate (or etomidate) with nitrous oxide and enflurane appears to be a suitable anesthetic for ventricular mapping and endocardial resection. The effects of enflurane on ventricular tachycardia induction and rate remain unknown.

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18 February 1992

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Balloon Cutting

In the article by Barath et al, "Cutting Balloon: A Novel Approach to Percutaneous Angio-

plasty" (*Am J Cardiol* 1991;68: 1249–1252), Barath states: "In this report we describe a new concept of angioplasty based on the premise that sharp incisions repair with less scar formation and remain more circumscribed than wounds created by tears. We produced sharp longitudinal surgical incisions radially in the media with our cutting balloon catheter."

With my colleagues, I first described internal longitudinal coronary artery incision for correction of coronary artery stenosis in 1966 ("A Method of Creating a Coronary-Myocardial Artery," *Surgery* 1966;59:1061–1064). This method was combined with the balloon dilating catheter and published in 1980 ("Coronary Artery Incision and Dilation," *Arch Surg* 1980; 115:1478–1480). I do not understand why Barath did not find these references, since they were published in major journals. I have written Barath (December 4, 1991) regarding these pertinent publications, but to this date I have had no reply.

Banning G. Lary, MD
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21 January 1992

REPLY: Lary deserves credit for his innovative idea of slicing through the stenosed coronary artery wall with a surgical knife into the myocardium to form a "coronary-myocardial artery" pocket. Further, his idea was proposed (*Surgery* 1966; 59:1061–1064) 13 years before Gruntzig, and only 2 years after Dotter. Lary's idea was neglected, and we contributed to this by not quoting him in our manuscript. Our method, of course, has differences (e.g., we are using a balloon system, and not trying to make holes on the coronary arteries). However, Lary's manuscript stands as a brilliantly innovative idea that was unfortunately ahead of its time.

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16 March 1992

More on Fast Foods and Quick Plaques

Five of every 10 dollars spent on restaurant food in the USA is spent at a fast-food restaurant. Each person in the USA spends an average of $250 a year on fast foods. Over 160,000 fast-food restaurants are available in the USA and $70,000,000,000 (10 zeros) are spent at them each year. The fast-food restaurants outnumber the traditional restaurants in the USA. McDonald's, the largest of the fast-food chains, has over 11,000 outlets and a new one goes up somewhere in the world every 15 hours. McDonald's is the largest owner of commercial real estate in the world, and they employ over 500,000 persons. One of 5 persons in the USA visits a fast-food restaurant everyday, and 4 of 5, every month. More than half of the fast-food business is done at drive-through windows. Fast-food restaurants are located in hospitals, zoos, military bases, college campuses (including dormitories), museums, airports, naval ships and boats (Mississippi River), bus stations, amusement parks, private-office and state-government buildings, and department stores. Mobile (restaurants on wheels) fast-food restaurants visit neighborhoods, playgrounds, and beaches. Menus are being diversified. McDonald's now offers more than 40 items. The top 15 fast-food chains spent $1,217,000,000 on advertising in 1989, directing many of their ads to children. Survey after survey shows that parents let their
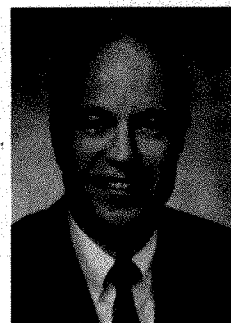
TABLE I Hamburgers and Cheeseburgers

Company/Product	Calories	Fat (tsp)	Sodium (mg)	Gloom
McDonald's Hamburger	255	2	490	16
Hardee's Hamburger	270	2	490	16
Burger King Hamburger	272	3	505	18
Jack in the Box Hamburger	267	3	556	18
McDonald's McLean Deluxe	320	2	670	18
McDonald's Cheeseburger	305	3	710	22
Hardee's Real Lean Deluxe	340	3	650	22
Burger King Cheeseburger	318	3	661	24
Burger King Burger Buddies	349	4	717	26
Burger King Hamburger Deluxe	344	4	496	27
Dairy Queen Single Hamburger with Cheese	365	4	800	29
McDonald's Quarter Pounder	410	5	650	31
Carl's Jr. Carl's Original Hamburger	460	5	810	31
Hardee's Big Twin	450	6	580	33
Dairy Queen Double Hamburger	460	6	630	37
Wendy's Double Hamburger	520	6	710	39
Jack in the Box Double Cheeseburger	467	6	842	40
Burger King Double Cheeseburger	483	6	851	40
McDonald's Big Mac	500	7	890	41
Hardee's Big Deluxe Burger	500	7	760	42
Hardee's Quarter-Pound Cheeseburger	500	7	1,060	42
McDonald's Quarter Pounder with Cheese	510	7	1,090	43
Burger King Bacon Double Cheeseburger	515	7	748	45
Wendy's Big Classic	570	7	1,085	48
Burger King Whopper	614	8	865	49
Jack in the Box Jumbo Jack	584	8	733	50
Hardee's Bacon Cheeseburger	610	9	1,030	54
Wendy's Big Classic with Cheese	640	9	1,345	56
Carl's Jr. Western Bacon Cheeseburger	730	9	1,490	59
Burger King Whopper with Cheese	706	10	1,177	61
Dairy Queen DQ Homestyle Ultimate Burger	700	11	1,110	63
Wendy's Double Big Classic	750	10	1,295	64
Burger King Double Whopper	844	12	933	72
Wendy's Double Big Classic with Cheese	820	12	1,555	72
Burger King Double Whopper with Cheese	935	14	1,245	83
Jack in the Box Ultimate Cheeseburger	942	16	1,176	88
Carl's Jr. Double Western Bacon Cheeseburger	1,030	14	1,810	91

Befriend your arteries by choosing small burgers and skipping the "special sauces." Cheeseburgers provide some calcium, but skim milk, yogurt, and green vegetables are much better, lower calorie sources.

The "Gloom" rating was designed by Jacobsen and Fritschner to give a quick summary of a food's or a meal's overall nutritional value. The formula for the Gloom rating provides 0.9 point/g of polyunsaturated oil; 1.1 point/g of highly saturated animal fat; 0.1 point/g of refined sugar or corn syrup; 1 point/20 mg of cholesterol; and 1 point/133 mg of sodium. This sum is then multiplied by a number ranging from 0.5 to 1.5 depending on the food's nutrient density, which is the ratio of nutrients/calorie (based on protein, calcium, iron, vitamin A, and vitamin C). For example, the multiplier would be 1 if a food contained 100% of the FDA of each of the 5 nutrients. Reprinted with permission of the publisher.

TABLE II Roast Beef

Company/Product	Calories	Fat (tsp)	Sodium (mg)	Gloom
Dairy Queen BBQ Beef Sandwich	225	1	700	10
Arby's Junior Roast Beef	218	2	345	16
Subway Roast Beef Sandwich, 6 in.	375	3	839	16
Arby's French Dip (roast beef sandwich)	345	3	678	20
Hardee's Roast Beef Sandwich (RR)	350	3	732	20
Hardee's Roast Beef Sandwich, large (RR)	373	3	840	21
Hardee's Regular Roast Beef	310	3	930	22
Arby's Regular Roast Beef	353	3	588	23
Hardee's Roast Beef Sandwich with Cheese (RR)	403	3	954	27
Hardee's Big Roast Beef	360	3	1,150	28
Hardee's Roast Beef Sandwich with Cheese, large (RR)	427	4	1,062	28
Arby's French Dip 'N Swiss (roast beef sandwich)	425	4	1,078	32
Arby's Beef 'N Cheddar	451	5	955	33
Carl's Jr. Roast Beef Deluxe Sandwich	540	6	1,340	38
Arby's Super Roast Beef	529	6	798	38
Arby's Philly Beef'N Swiss	498	6	1,194	40
Arby's Giant Roast Beef	530	6	908	40
Arby's Bac 'N Cheddar Deluxe	532	7	1,672	52

Plain roast beef is lower in fat than most hamburger meat, but a sandwich, topped with bacon, cheese, or sauces, may be quite fatty. Hardee's sandwiches marked "(RR)" are available in the New York-Washington region; they are made from the very lean roast beef that has been used by Roy Rogers restaurants. Reprinted with permission of the publisher.

children make restaurant choices. When children under age 17 years eat at a restaurant in the USA, 83% of the time it is at a fast-food chain.

The above information comes from the second edition of the *FAST-FOOD GUIDE* published in 1991 and written by Michael F. Jacobson, PhD, Executive Director, Center for Science in the Public Interest, and Sarah Fritschner, a nutritionist and the food editor of the Louisville *Courier-Journal*.[1] Like their first edition, which appeared in 1986[2] (and also reviewed in this column[3]), this new book details the amounts of calories, fat, sodium, sugar, and other "nutrients" in the foods and liquids sold by the 15 largest fast-food chains in the USA (Tables I to VII). When Jacobson and Fritschner wrote their 1986 book, virtually all fast-food chains were resistant to supplying them with the ingredients of the products sold. For their 1991 book, in contrast, most chains freely supplied them the ingredients of the products.

TABLE III Chicken and Turkey

Company/Product	Calories	Fat (tsp)	Sodium (mg)	Gloom
Carl's Jr. Charbroiler BBQ Chicken Sandwich	310	1	680	12
Arby's Light Roast Chicken Deluxe	253	1	874	13
Long John Silver's Chicken Plank, 1 piece	130	1	490	13
Jack in the Box Chicken Fajita Pita	292	2	703	14
KFC Original Recipe Drumstick	146	2	275	14
Hardee's Chicken Stix, 6 pieces	210	2	680	15
Burger King BK Broiler Chicken Sandwich	267	2	728	15
Dairy Queen Grilled Chicken Fillet Sandwich	300	2	800	16
Subway Turkey Sandwich, 6 in.	357	2	839	16
Wendy's Grilled Chicken Sandwich	320	2	715	16
Long John Silver's Baked Chicken Sandwich (no sauce)	320	2	900	17
KFC Original Recipe Wing	178	3	372	18
Burger King Chicken Tenders, 6 pieces	236	3	541	21
KFC Extra Tasty Crispy Drumstick	204	3	324	22
Hardee's Chicken Fillet	370	3	1,060	24
KFC Original Recipe Center Breast	283	3	672	25
Arby's Grilled Chicken Barbecue	378	3	1,059	25
Wendy's Chicken Sandwich, fried	430	4	725	25
KFC Original Recipe Side Breast	267	4	735	27
Arby's Turkey Deluxe	399	5	1,047	28
Jack in the Box Grilled Chicken Fillet	408	4	1,130	28
KFC Extra Tasty Crispy Wing	254	4	422	30
McDonald's McChicken	415	7	770	30
Wendy's Crispy Chicken Nuggets, 6 pieces	280	5	600	31
Dairy Queen Breaded Chicken Breast Fillet Sandwich	430	5	760	32
KFC Original Recipe Thigh	294	4	619	33
KFC Hot Wings, 6 pieces	376	5	677	40
Arby's Roast Chicken Club	513	7	1,423	43
KFC Colonel's Chicken Sandwich	482	6	1,060	45
KFC Extra Tasty Crispy Thigh	406	7	688	48
Arby's Chicken Cordon Bleu	658	8	1,824	60
Burger King Chicken Sandwich	685	9	1,417	61

Chicken starts out lean and wholesome, but once it is battered, breaded, fried, and smothered with a mayonnaise sauce, it will be loaded with fat and calories. Look for baked or broiled chicken, hold the sauces, and discard the grease-soaked breading.
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TABLE IV Fish

Company/Product	Calories	Fat (tsp)	Sodium (mg)	Gloom
Long John Silver's Shrimp, battered, 1 piece	60	1	180	7
Long John Silver's Fish, Homestyle, 1 piece	125	2	200	8
Wendy's Seafood Salad	110	2	455	9
Subway Tuna Sandwich, 6 in.	402	3	905	17
Long John Silver's Clams, breaded	240	3	410	19
Subway Seafood and Crab Sandwich, 6 in.	388	3	1,306	20
Long John Silver's Fish, battered, 1 piece	210	2	570	21
Dairy Queen Fish Fillet Sandwich	370	4	630	26
McDonald's Filet-O-Fish	370	6	930	32
Dairy Queen Fish Fillet Sandwich with Cheese	440	5	880	33
Burger King Ocean Catch Fish Filet	495	6	879	37
Wendy's Fish Fillet Sandwich	460	6	780	38
Hardee's Fisherman's Fillet	500	5	1,030	38
Jack in the Box Fish Supreme	510	6	1,040	41
Arby's Fish Fillet Sandwich	537	7	994	46
Carl's Jr. Carl's Catch Fish Sandwich	560	7	1,220	47

Most fresh fish is low in fat and quite healthful. But most fast-food fish is deep-fried and as fatty as many hamburgers. Seek broiled or baked fish, and season with lemon juice instead of butter and tartar sauce.
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TABLE V French Fries

Company/Product	Calories	Fat (tsp)	Sodium (mg)	Gloom
Long John Silver's Fryes (3 oz.)	170	2	55	7
Dairy Queen, small (2.5 oz.)	210	2	115	13
Hardee's, regular (2.5 oz.)	230	3	85	14
Jack in the Box, small (2.5 oz.)	219	3	121	14
McDonald's, small (2.4 oz.)	220	3	110	16
KFC (2.5 oz.)	244	3	139	16
Arby's, small (2.5 oz.)	246	3	114	18
Hardee's, large (4 oz.)	360	4	135	21
Wendy's, large (4.2 oz.)	312	4	189	22
Jack in the Box, regular (4 oz.)	351	4	194	22
McDonald's, medium (3.4 oz.)	320	4	150	23
Dairy Queen, large (4.5 oz.)	390	4	200	24
Jack in the Box, Jumbo (5 oz.)	396	5	219	24
Arby's Curly Fries (3.5 oz.)	337	4	167	27
Hardee's Crispy Curls (3 oz.)	300	4	840	27
Carl's Jr., regular (4.5 oz.)	420	5	200	29
McDonald's, large (4.3 oz.)	400	5	200	29
Arby's, medium (4 oz.)	394	5	182	29
Burger King, medium (4 oz.)	372	5	238	30
Hardee's, "Big Fry" (5.5 oz.)	500	5	180	30
Wendy's, Biggie (6 oz.)	449	5	271	32
Arby's Cheddar Fries (5 oz.)	399	5	443	35
Arby's, large (5 oz.)	492	6	228	37

Though they're deep-fried and salted, french fries are not quite as bad as their reputation would have them. But a small serving should be more than enough, and ask the clerk to hold the salt. Kudos to Long John Silver's for making salt-free "Fryes" its standard.
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TABLE VI Shakes and Malts					
Company/Product	Calories	Fat (tsp)	Sodium (mg)	Sugar (tsp)	Gloom
McDonald's, Low-fat (average)	310	<1	193	9	7
Carl's Jr., regular	350	2	230	10	14
Jack in the Box (average)	323	2	247	10	15
Hardee's (average)	433	2	320	12	19
Arby's, Vanilla	330	3	281	7	20
Arby's, Jamocha	368	2	262	8	20
Arby's Chocolate	451	3	341	12	24
Dairy Queen Malt, regular	610	3	230	9	25
Burger King Chocolate, large	472	3	286	12	26
Dairy Queen Shake, regular	520	3	230	11	26
Dairy Queen Shake, large	600	4	260	13	30
Wendy's Frosty Dairy Dessert, medium	520	4	286	7	30
Arby's Snickers Polar Swirl	511	4	351	9	33
Wendy's Frosty Dairy Dessert, large	680	5	374	9	40
Arby's Peanut Butter Cup Polar Swirl	517	5	385	14	41
Dairy Queen Heath Blizzard, regular	820	8	410	14	58

Typical shakes contain about as much sugar (figures shown are estimates) as a can of cola, as much fat as a glass of milk, and as many calories as a cola and milk combined. However, they are all good sources of calcium. McDonald's was first to offer a low-fat shake. For some companies, the average of several flavors is shown.
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TABLE VII Salads				
Company/Product	Calories	Fat (tsp.)	Sodium (mg)	Gloom
Arby's Side Salad	25	0	30	0
Wendy's Garden Salad	70	<1	60	1
Burger King Chunky Chicken Salad	142	1	443	6
McDonald's Chunky Chicken Salad	150	1	230	6
Wendy's Chef Salad	180	2	140	10
Subway Turkey Salad, small	167	2	479	10
Long John Silver's Seafood Salad	230	2	580	10
Subway Roast Beef Salad, small	185	2	479	11
McDonald's Chef Salad	170	3	400	12
Subway Tuna Salad, small	212	3	545	12
Burger King Chef Salad	178	2	568	13
Carl's Jr. Charbroiler Chicken Salad	200	2	300	15
Hardee's Garden Salad	210	3	270	15
Long John Silver's Ocean Chef Salad	250	2	1,340	17
Hardee's Chicken Fiesta Salad	280	3	640	19
Hardee's Chef Salad	240	3	930	20
Jack in the Box Chef Salad	325	4	900	25
Taco Bell Taco Salad, no shell	484	7	680	34
Wendy's Taco Salad	660	8	1,110	39
Taco Bell Taco Salad, with shell	905	14	910	68

Most salads, other than taco salads, are low in calories and fat. Be sure to ask for a low-calorie dressing or you risk ruining a good thing with several hundred additional calories.
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From 1986 to 1991, the 5-year period between the 2 editions of the 2 fast food books, most, but not all, of the fast-food chains decreased the calorie, fat and sodium contents of their foods. Several (McDonald's, Burger King, Hardee's, Arby's, Dairy Queen, Jack in the Box, and Wendy's) switched from beef fat to vegetable shortening for all frying, and 1 (Taco Bell) switched from coconut oil (92% saturated) to a less saturated vegetable shortening for all frying. McDonald's became the first chain to offer 1% low-fat milk and breakfast cereals. Frozen and non-fat yogurt was introduced by McDonald's and Baskin-Robbins. Wendy's dropped completely the Triple Cheeseburger from its menus. This hamburger/cheeseburger was number 1 for calories (1,040), fat (15 teaspoons), and sodium (1,848 mg) in 1986. Today's worst is Carl's Jr. Double Western Bacon Cheeseburger which contains 1,030 calories, 14 teaspoons of fat and 1,810 mg of sodium (Table I). Several (Arby's, Dunkin' Donuts, and Hardee's) either switched to cholesterol free or to a lower calorie mayonnaise. Despite these type changes, the saturated fat and cholesterol contents of the fast-food products remain far too high. Most changes, however, are in the right direction, and many others can be expected by the time the Jacobson/Fritschner third edition appears.
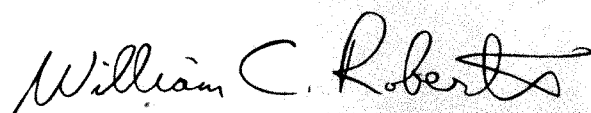
Congratulations to Jacobson and Fritschner for keeping the pressure on the fast-food suppliers to supply us with more healthy foods and liquids.

William Clifford Roberts, MD
Editor in Chief

1. Jacobson MF, Fritschner S. The Completely Revised and Updated Fast-Food Guide, Second Edition. New York: Workman Publishing, 1991:333.
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Accupril® (Quinapril Hydrochloride Tablets)

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ACCUPRIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Before prescribing, please see full prescribing information. A brief summary follows.

INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nevertheless, when patients become pregnant, physicians should make every effort to discontinue the use of ACCUPRIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ACCUPRIL should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Removal of ACCUPRIL, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means.

No teratogenic effects of ACCUPRIL were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 180 times (in rats) and one time (in rabbits) the maximum recommended human dose.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told not to take the drug again until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an

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excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:
- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: in vitro mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, in vitro chromosome aberration with V79 cultured lung cells, and in an in vivo cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

See PRECAUTIONS, Cough.

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, nervousness, *depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Fetal/Neonatal Morbidity and Mortality

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (77.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

*To obtain the optimal antihypertensive effect in patients with mild to moderate hypertension, dosage adjustments should generally be made at intervals of at least 2 weeks.

SINGLE-AGENT THERAPY*

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